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(71) Applicant(s)
Shionogi and Co., Ltd.

(72) Inventor(s)
Mitsuaki Ohtani; Toshiyuki Kato; Fumihiko Watanabe; Kaoru Seno

(74) Agent/Attorney
DAVIES COLLISON CAVE, 1 Little Collins Street, MELBOURNE VIC 3000

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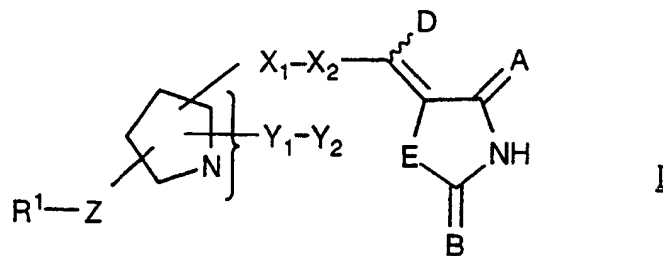


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<p>(51) 国際特許分類6 C07D 417/12, 417/14, 413/12, A61K 31/42, 31/425, 31/44, 31/47</p>	<p>A1</p>	<p>(11) 国際公開番号 WO97/05135</p> <p>(43) 国際公開日 1997年2月13日(13.02.97)</p>
<p>(21) 国際出願番号 PCT/JP96/02079</p> <p>(22) 国際出願日 1996年7月25日(25.07.96)</p> <p>(30) 優先権データ 特願平7/194648 1995年7月31日(31.07.95) JP</p> <p>(71) 出願人 (米国を除くすべての指定国について) 塩野義製薬株式会社(SHIONOGI & CO., LTD.)[JP/JP] 〒541 大阪府大阪市中央区道修町三丁目1番8号 Osaka, (JP)</p> <p>(72) 発明者：および</p> <p>(75) 発明者／出願人 (米国についてのみ) 大谷光昭(OHTANI, Mitsuaki)[JP/JP] 〒630 奈良県奈良市高畑町1342 Nara, (JP) 加藤利幸(KATO, Toshiyuki)[JP/JP] 〒565 大阪府吹田市千里丘下25-17 Osaka, (JP) 渡邊文彦(WATANABE, Fumihiko)[JP/JP] 〒639-02 奈良県北葛城郡上牧町友が丘2丁目5-22 Nara, (JP) 瀬野 薫(SENO, Kaoru)[JP/JP] 〒663 兵庫県西宮市樋ノ口町1丁目10番19号 Hyogo, (JP)</p>	<p>(74) 代理人 弁理士 青山 稔, 外(AOYAMA, Tamotsu et al.) 〒540 大阪府大阪市中央区城見1丁目3番7号 IMPビル 青山特許事務所 Osaka, (JP)</p> <p>(81) 指定国 AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO特許 (KE, LS, MW, SD, SZ, UG), ユーラシア特許 (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), 欧州特許 (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI特許 (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).</p> <p>添付公開書類 国際調査報告書</p>	
<p>(54)Title: PYRROLIDINE DERIVATIVES HAVING PHOSPHOLIPASE A₂ INHIBITORY ACTIVITY</p> <p>(54)発明の名称 ホスホリパーゼA₂阻害活性を有するピロリジン誘導体</p> <div data-bbox="565 1329 1027 1505" data-label="Chemical-Block"> <p style="text-align: center;">(I)</p> </div> <p>(57) Abstract Compound represented by general formula (I) or pharmaceutically acceptable salts or hydrates thereof, having the activity of inhibiting the production of prostaglandin E₂ by inhibiting intracellular phospholipase A₂.</p>		

(57) 要約

式I:



で示される化合物もしくは製薬的に許容されるその塩又はその水和物であって、細胞内ホスホリパーゼA₂阻害活性によるプロスタグランジンE₂の産生阻害活性を有する化合物。

情報としての用途のみ

PCTに基づいて公開される国際出願をパンフレット第一頁にPCT加盟国を同定するために使用されるコード

AL	アルバニア	DE	ドイツ	LI	リヒテンシュタイン	PL	ポーランド
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CZ	チェコ共和国	KR	大韓民国	NO	ノルウェー	US	アメリカ合衆国
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						VN	ヴェトナム

DESCRIPTION

PYRROLIDINE DERIVATIVES HAVING PHOSPHOLIPASE A₂ INHIBITORY
ACTIVITY

5

TECHNICAL FIELD

The present invention relates to novel pyrrolidine derivatives having an activity of inhibiting cytosolic phospholipase A₂, and pharmaceutical compositions for inhibiting
10 the cytosolic phospholipase A₂ which contain a novel pyrrolidine derivative as an active ingredient.

BACKGROUND ART

Phospholipase A₂ (PLA₂) is a protein capable of
15 specifically hydrolyzing 2-acyl ester bond(s) of phospholipids, and includes cytosolic PLA₂ (cPLA₂) and secretory type PLA₂ (sPLA₂) which are clearly distinguishable.

It is known that cPLA₂ can selectively hydrolyze phospholipids containing arachidonic acid which is esterified at
20 the 2-position. Accordingly, the prevention of cPLA₂ activity would inhibit the release of arachidonic acid from phospholipids. Arachidonic acid is a precursor of prostaglandins and leukotrienes, which are biological substances known to be participating in the onset of inflammation. These inflammatory substances are produced
25 through a series of processes so called "arachidonate cascade". Therefore, the inhibition of the release of arachidonic acid would suppress the activity of various substances involved in inflammation and is useful in the prevention or treatment of

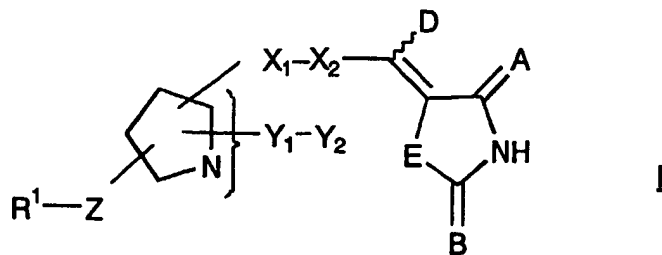


inflammatory diseases. Examples of such disease include rheumatoid arthritis, asthma, inflammatory bowel disease, injury due to ischemic reperfusion, allergic rhinitis, and psoriasis.

However, there have not been provided any substances which have highly specific activity of inhibiting cPLA₂ and are clinically applicable. It has been disclosed that compounds having phenoxy group between thiazolidione and pyrrolidine rings, which pyrrolidine ring is substituted at the N-atom with benzoxazole, etc., are effective on non-insulin dependent diabetes, or the like. See, Japanese Patent Publication (KOKAI) No. 213913/1993 corresponding to France Patent Application, Priority Claiming No. 9110430, Priority date: Aug. 20, 1991. However, there is no description about compounds having phospholipase A₂ inhibitory activity in the said literature.

DISCLOSURE OF INVENTION

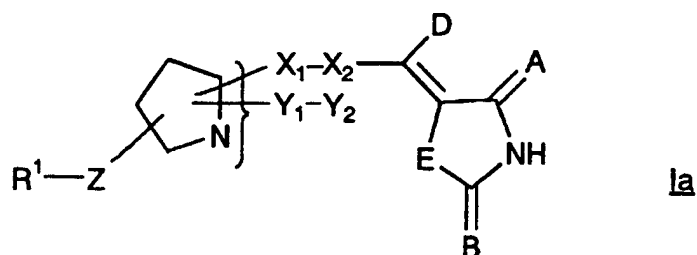
The present inventors have intensively studied for developing specific cPLA₂ inhibitors and found that certain kinds of novel pyrrolidine derivatives, especially those having partial structure of thiazolidinedione or oxazolidinedione, possess a potent cPLA₂ inhibitory activity. Thus, the present invention provides a compound of the formula I:



wherein A and B are independently O or S; E is O or S; X_1 is -CO-, -CONH-, -CH₂NHSO₂-, -CH₂NHCO-, -CH₂NHCS-, -CH₂O-, -OCH₂-, -CH₂OCH₂-, alkylene, alkenylene or a single bond; X_2 is optionally substituted arylene, optionally substituted indol-diyl or a single bond; D is hydrogen or hydroxyalkyl; Y_1 is -(CH₂)_mCO-, -(CH₂)_nNHCO-, -(CH₂)_nNHSO₂-, -(CH₂)_mCONH-, -(CH₂)_mCSNH-, -(CH₂)_nSO₂-, -(CH₂)_nCOO-, or a single bond; m and n are an integer of 0 to 3; Y_2 is hydrogen, alkyl, optionally substituted alkenyl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted cycloalkylalkyl, optionally substituted cycloalkenylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heterocyclic group or optionally substituted amino; Z is -S-, -SO-, -O-, -NH-, -CONH-, -CONHCH₂- or a single bond; R¹ is hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted aryl or optionally substituted aralkyl, or a pharmaceutically acceptable salt or a hydrate thereof, provided that when X_1 is -CH₂O-, Y_1 is not a single bond; Y_1 binds to the pyrrolidine ring at 1- or 2-position, X_1 binds to any positions other than the one to which Y_1 binds (provided that when Y_1 is at the 2-position, X_1 binds to the 1-position), and Z binds to any one of carbon atoms on the pyrrolidine ring other than those to which X_1 and Y_1 bind; when Y_1 binds to the N-atom on the pyrrolidine ring, n is not 0; when Y_1 is -(CH₂)_nCOO- and m is 0, Y_2 is not H; and when X_1 is -OCH₂-, it does not bind to the N-atom on the pyrrolidine ring.

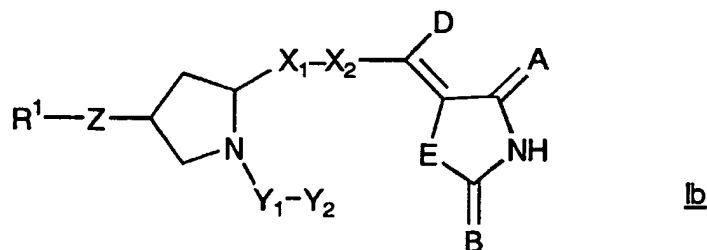
For purposes of the present invention, all the compounds as defined above are preferred. However, compounds of preferred embodiment are shown by the formula Ia:





5 wherein A, B, E, X₁, X₂, D, Y₁, Y₂, Z and R¹ are as defined above,
 or a pharmaceutically acceptable salt or a hydrate thereof,
 provided that when X₁ is -CH₂O-, Y₁ is not a single bond; Y₁ binds
 to the pyrrolidine ring at the 1- or 2-position and when Y₁ binds
 to the 1-position, X₁ binds to the 2-position and when Y₁ binds to
 10 the 2-position, X₁ binds to the 1-position, and Z binds to any one
 of carbon atoms on the pyrrolidine ring other than those to which
 X₁ and Y₁ bind; when Y₁ binds to the N-atom on the pyrrolidine ring,
 n is not 0; when Y₁ is -(CH₂)_mCOO- and m is 0, Y₂ is not H; and when
 X₁ is -OCH₂-, it does not bind to the N-atom on the pyrrolidine ring.

15 Specific examples include a compound of the formula Ib:



20

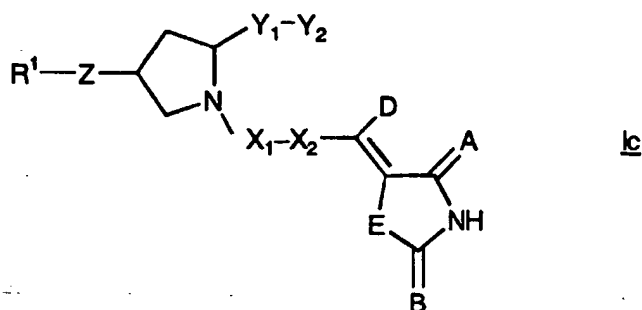
wherein A, B, E, X₁, X₂, D, Y₁, Y₂, Z and R¹ are as defined above,
 or a pharmaceutically acceptable salt or a hydrate thereof,
 provided that when X₁ is -CH₂O-, Y₁ is not a single bond; n is not
 0; when Y₁ is -(CH₂)_mCOO- and m is 0, Y₂ is not H.

25

Similarly, examples include a compound of the formula



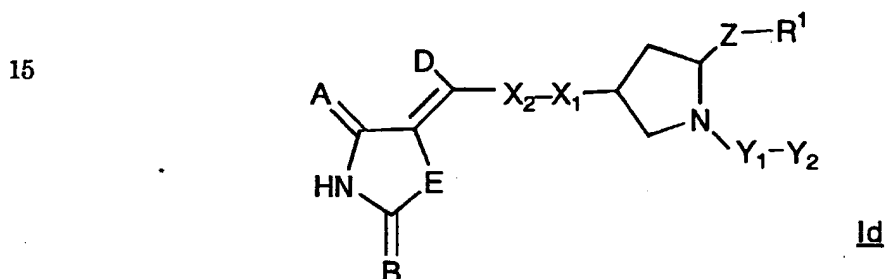
Ic:



wherein A, B, E, X₁, X₂, D, Y₁, Y₂, Z and R¹ are as defined above,
 or a pharmaceutically acceptable salt or a hydrate thereof,
 10 provided that when X₁ is -CH₂O-, Y₁ is not a single bond; when X₁
 is -OCH₂-, it does not bind to the N-atom on pyrrolidine ring.

Similarly, examples include a compound of the formula

Id:



wherein A, B, E, X₁, X₂, D, Y₁, Y₂, Z and R¹ are as defined above,
 20 or a pharmaceutically acceptable salt or a hydrate thereof,
 provided that when X₁ is -CH₂O-, Y₁ is not a single bond; n is not
 0; when Y₁ is -(CH₂)_mCOO- and m is 0, Y₂ is not H. Examples of a
 compound of more preferred embodiments are as follows.

- 1) A compound wherein E is S, and A and B are O, or a
 25 pharmaceutically acceptable salt or a hydrate thereof.
- 2) A compound wherein X₁ is -CONH-, -CH₂NHSO₂- or -CH₂NHCO-, or
 a pharmaceutically acceptable salt or a hydrate thereof.
- 3) A compound wherein X₂ is optionally substituted phenylene,



or a pharmaceutically acceptable salt or a hydrate thereof.

- 4) A compound wherein Y_1 is $-CO-$, $-CONH-$ or $-SO_2-$, or a pharmaceutically acceptable salt or a hydrate thereof.
- 5) A compound wherein Y_2 is optionally substituted
 5 cycloalkenylalkyl, optionally substituted aryl, optionally substituted aralkyl or optionally substituted heterocyclic group, or a pharmaceutically acceptable salt or a hydrate thereof.
- 6) A compound wherein Z is $-S-$ or $-O-$, or a pharmaceutically
 10 acceptable salt or a hydrate thereof.
- 7) A compound wherein R^1 is optionally substituted alkyl or optionally substituted aralkyl, or a pharmaceutically acceptable salt or a hydrate thereof.

The term "alkyl" means $C_1 - C_{15}$ straight or branched
 15 chain alkyl, for example, methyl, ethyl, propyl, n-butyl, i-butyl, t-butyl, n-pentyl, n-hexyl, i-hexyl, n-heptyl, t-heptyl, i-heptyl, n-octyl, i-octyl, 3,7-dimethyloctyl, n-nonyl, n-decyl, n-undecyl, n-dodecyl, and the like. The alkyl may have one or more substituents selected from the group consisting of halogen, alkoxy,
 20 oxo, phenyl (e.g., 4-nitrophenyl, 4-methoxyphenyl) and phenylsulfonyl.

The term "alkenyl" means $C_2 - C_{10}$ straight or branched chain alkenyl, for example, vinyl, allyl, propenyl, and the like. The alkenyl may have one or more substituents selected from the
 25 group consisting of halogen, alkoxy and phenyl. The phenyl may also have a substituent(s), for example, halogen, alkoxy, alkylendioxy, and the like.

Examples of "hydroxyalkyl" include hydroxymethyl,



hydroxyethyl, and the like, and hydroxymethyl is preferred.

The term "cycloalkyl" means $C_3 - C_{12}$ cycloalkyl, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and the like.

5 The term "cycloalkylalkyl" refers to a group wherein alkyl group is substituted with $C_3 - C_{12}$ cycloalkyl group, for example, cyclopropylmethyl, cyclobutylmethyl, cyclopentylethyl, and the like.

 The term "cycloalkenyl" means $C_3 - C_{12}$ cycloalkenyl, for
10 example, cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclopentadienyl (e.g., 1,3-cyclopentadien-1-yl), cyclohexadienyl (e.g., 1,4-cyclohexadien-1-yl), and the like.

 The term "cycloalkenylalkyl" refers to a group wherein alkyl group is substituted with $C_3 - C_{12}$ cycloalkenyl group, for
15 example, cyclopropenylmethyl, cyclobutenylethyl, cyclopentanylmethyl, cyclopentadienylmethyl, cyclohexadienylhexyl (e.g., 1,4-cyclohexadienylhexyl), dihydronaphthylhexyl (e.g., 1,4-dihydronaphthylhexyl), and the like.

20 The substituent(s) on the above-mentioned "cycloalkyl", "cycloalkenyl", cycloalkylalkyl" and "cycloalkenylalkyl" is the same as that described in the definition for "alkyl".

 The term "optionally substituted amino" means mono- or di-substituted amino or cyclic amino, for example, dimethylamino,
25 diethylamino, ethylmethylamino, morpholino, piperidino, piperadino, and the like.

 The term "alkylene" means a group derived from $C_1 - C_4$ alkyl, for example, methylene, ethylene, trimethylene and



tetramethylene.

The term "alkenylene" means a group derived from $C_2 - C_4$ alkenyl, for example, vinylene, propenylene and butenylene.

The term "aryl" refers to, for example, phenyl, naphthyl, and the like, and phenyl is preferred. The aryl may have one or more substituents selected from the group consisting of phenyl, halogen, alkyl, alkoxy, trifluoromethyl, alkylendioxy, acyl, carboxy, alkoxycarbonyl, carbamoyl, hydroxymethyl, amino, nitrile and benzhydryl, acylamino (e.g., acetylamino), cyanoalkoxy (e.g., 3-cyanopropoxy), phenylazo, arylsulfonyl (e.g., phenylsulfonyl), nitro, aralkyl (e.g., benzyl), 3-oxoisothiazolin-2-yl, 2-oxopyrrolidin-1-yl, cyanothiocarbonylamino, 1,1,3-trioxo-1,2-benzisothiazol-2-ylmethoxy, t-butyldimethylsilyl, hydroxy, acyloxy (e.g., acetyloxy), oxo, 2-oxoisothiazolin-2-ylmethyl, alkoxycarbonylamino (e.g., t-butyloxycarbonylamino), alkoxycarbonyl (e.g., methoxycarbonyl), alkoxycarbonylalkyl (e.g., methoxycarbonylethyl) and hydroxyalkyl (e.g., hydroxypropyl). Examples of preferred substituents include carboxy, carbamoyl, halogen, methyl, methoxy, trifluoromethyl, and the like. Accordingly, examples of aryl include 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2,3-difluorophenyl, 2,6-difluorophenyl, 4-chlorophenyl, 2,4-dichlorophenyl, 2,6-dichlorophenyl, 4-bromophenyl, 2,4-dibromophenyl, 4-methylphenyl, 4-ethylphenyl, 4-t-butylphenyl, 3,5-di-t-butylphenyl, 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 2,3-dimethoxyphenyl, 2,6-dimethoxyphenyl, 2,4-dimethoxyphenyl, 3,4-dimethoxyphenyl, 3,5-dimethoxyphenyl, 3,4-



methylenedioxyphenyl, 3,4-ethylenedioxyphenyl, 2-acetylphenyl, 3-acetylphenyl, 4-acetylphenyl, 4-acetylamino-phenyl, 4-acetylamino-3,5-dichlorophenyl, 2-carboxyphenyl, 3-carboxyphenyl, 4-carboxyphenyl, 2-methoxycarbonylphenyl, 3-methoxycarbonylphenyl, 4-methoxycarbonylphenyl, 2-ethoxycarbonylphenyl, 3-ethoxycarbonylphenyl, 4-ethoxycarbonylphenyl, 2-carbamoylphenyl, 3-carbamoylphenyl, 4-carbamoylphenyl, 4-benzhydrylphenyl, 4-trifluoromethylphenyl, 4-N,N-dimethylaminophenyl, 4-phenylazophenyl, 4-benzylphenyl, 5-dimethylamino-1-naphthyl, 1,4-dihydro-2-naphthyl, and the like.

The definition of aryl includes not a group containing a single aryl group but also a group containing two or more aryl groups in series such as diphenyl group.

The term "arylene" means, for example, phenylene and naphthalene such as 1,2-phenylene, 1,3-phenylene, 1,4-phenylene, and the like.

The substituents on the aryl of "arylene" or "indol-diyl" can be the same as those on "aryl".

The term "aralkyl (arylalkyl)" is a group formed by substituting an alkyl with an aryl as defined above. Examples include benzyl, phenethyl, and the like. The aryl moiety in the arylalkyl may have substituents as mentioned above. Accordingly, examples of aralkyl include benzyl, 1-naphthylmethyl, 2-naphthylmethyl, 4-methylphenylmethyl, 2,4,6-trimethylphenylmethyl, 3,5-di-t-butyl-4-methoxyphenyl, biphenylmethyl, 4-fluorophenylmethyl, 4-bromophenylmethyl, 4-chlorophenylmethyl, 2,6-dichlorophenylmethyl, 2,4-difluorophenylmethyl, 4-



- trifluorophenylmethyl, 2,4-ditrifluorophenylmethyl, 2-methyl-4-trifluorophenylmethyl, 4-methoxyphenylmethyl, 3,4,5-trimethoxyphenylmethyl, 4-methoxycarbonylphenylmethyl, 4-carboxyphenylmethyl, 4-carbamoylphenylmethyl, 4-
- 5 cyanopropoxyphenylmethyl, 4-nitrophenylmethyl, benzhydryl, di-(4'-fluorophenyl)methyl, triphenylmethyl, and the like.

The term "heterocyclic group" means a cyclic group containing one or more hetero atoms selected from the group consisting of oxygen, sulfur or nitrogen atom on the ring, and is

10 optionally condensed with a carbon ring. Examples include pyrrolyl (e.g., 2-pyrrolyl), indolyl (e.g., 2-indolyl), isoindolyl (e.g., 3-isoindolyl), pyrazolyl (e.g., 4-pyrazolyl), carbazolyl (e.g., 5-carbazolyl), quinolyl (e.g., 8-quinolyl), benzimidazolyl (e.g., 5-benzimidazolyl), phenoxathiinyl (e.g.,

15 2-phenoxathiinyl), phenoxazinyl (e.g., 3-phenoxazinyl), benzisoxazolyl (e.g., 1,2-benzisoxazol-1-yl), benzothiazolyl (e.g., 2-benzothiazolyl), benzoxazolyl (e.g., 6-benzoxazolyl), pyridyl (e.g., 2-pyridyl), thiazolyl (e.g., 5-thiazolyl), azetidyl (e.g., azetidin-2-yl), and the like.

20 The substituent on the "optionally substituted-heterocyclic group" can be the same as those for aryl.

The term "halogen" means fluorine, chlorine, bromine, and iodine.

Examples of pharmaceutically acceptable salts include

25 salts formed with an alkali metal such as potassium or sodium, an alkali earth metal such as calcium, or the like.

Further, the compound of the present invention and its salt can form a hydrate.



THE BEST EMBODIMENT FOR PRACTICING THE INVENTION

Although the compound I of the present invention can be prepared in a conventional manner, it is conveniently prepared according to either of the processes shown below depending on the type of the aimed compounds. The following processes are, however, provided just for illustrative purpose and compounds I prepared by any other methods also fall within the scope of the invention.

- 1) Compounds having sulfur atom at the 4-position of pyrrolidine ring ($Z = -S-$)

Method A: Compounds having amide group at the 2-position of pyrrolidine ring ($X_1 = -CONH-$).

- Method B: Compounds having alkylene group at the 2-position of pyrrolidine ring.

Method B₁: Compounds having amide or sulfonamide group at the 2-position of pyrrolidine ring via alkylene group ($X_1 = -CH_2NHCO-$, $-CH_2NHSO_2-$ or $-CH_2NHCS-$).

- Method B₂: Compounds having thiazolidinedione group at the 1-position of pyrrolidine ring ($X_1 = -CO-$).

Method C: Compounds wherein thiazolidinedione is substituted at a different position(s) ($X_1 = -CONH-$).

Method D: Compounds having hydroxyalkyl group on double bond ($D = \text{hydroxyalkyl}$).

- Method E₁: Compounds which do not have an amide bond at the 2-position of pyrrolidine ring but have a carbon- or ether-bond directly linked thereto ($X_1 = -CH_2OCH_2-$ or $-CH_2O-$).

Method E₂: Compounds having carbon bond at the 2-position of



pyrrolidine ring (X_1 is alkylene or alkenylene).

Method F: Compounds having thiazolidinedione at the 2-position of pyrrolidine ring (X_1 = single bond, X_2 = single bond).

- 5 2) Compounds having oxygen atom at the 4-position of pyrrolidine ring (Z = -O-).

Method G: Compounds having amide group at the 2-position of pyrrolidine ring (X_1 = -CONH-).

- 10 Method H: Compounds having alkylene group at the 2-position of pyrrolidine ring (X_1 = -CH₂NHCO-, -CH₂NHSO₂- or -CH₂NHCS-).

Method I: Compounds having hydroxyalkyl group on the double bond (D = hydroxyalkyl).

- 15 3) Compounds having nitrogen atom at the 4-position of pyrrolidine ring (Z = -NH- or -CONH-).

Method J

- 4) Compounds having carbon atom at the 4-position of pyrrolidine ring (Z = single bond).

20 Method K

- 5) Proline derivative (Z = single bond, R^1 = hydrogen)

Method L: Compounds wherein pyrrolidine ring has no substituents at the 4-position.

25

- 6) Compounds having sulfur atom at the 4-position of pyrrolidine ring and exhibiting different configuration at the 2- and 4-positions of pyrrolidine ring.

Method M: Compounds of the configuration of (2 β , 4 α), (2 α , 4 β) or



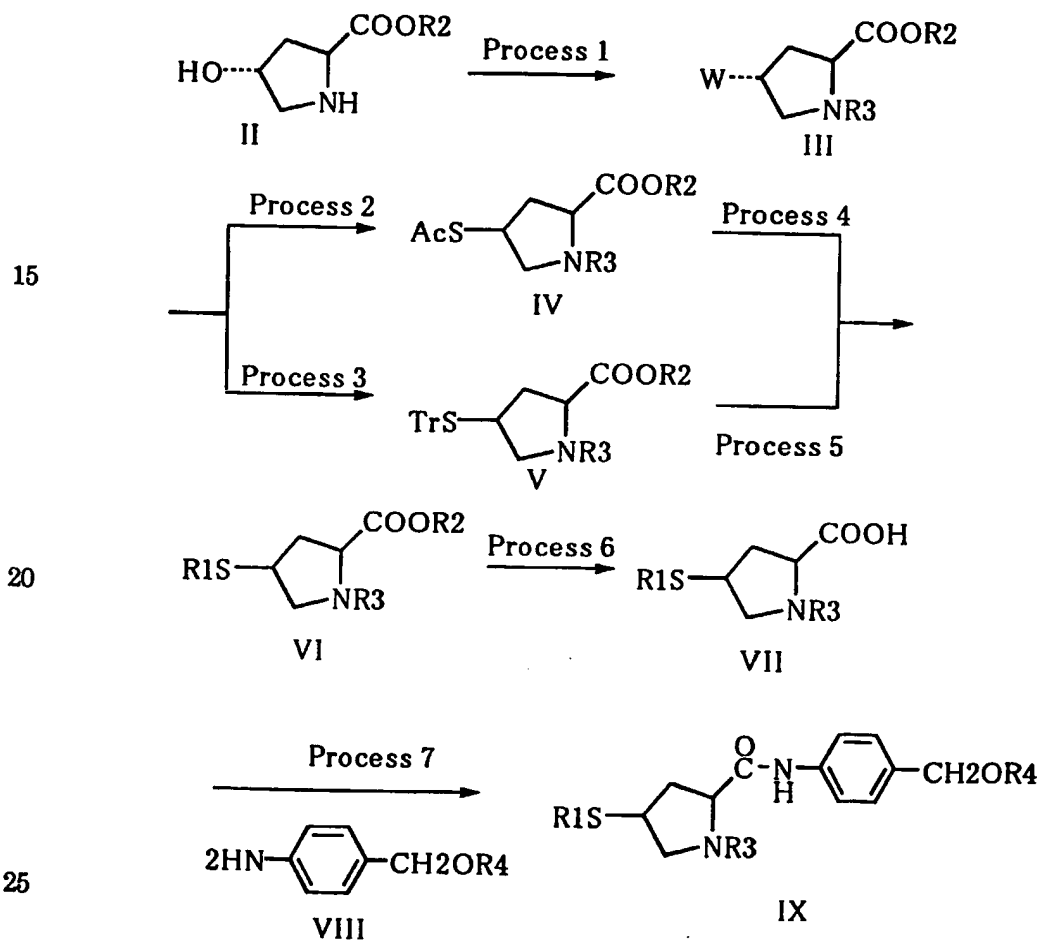
(2 α , 4 α) having sulfur atom at the 4-position of pyrrolidine ring. Compounds having sulfur atom at the 4-position of pyrrolidine ring prepared according to the method of item 1) above are in (2 β , 4 β) configuration.

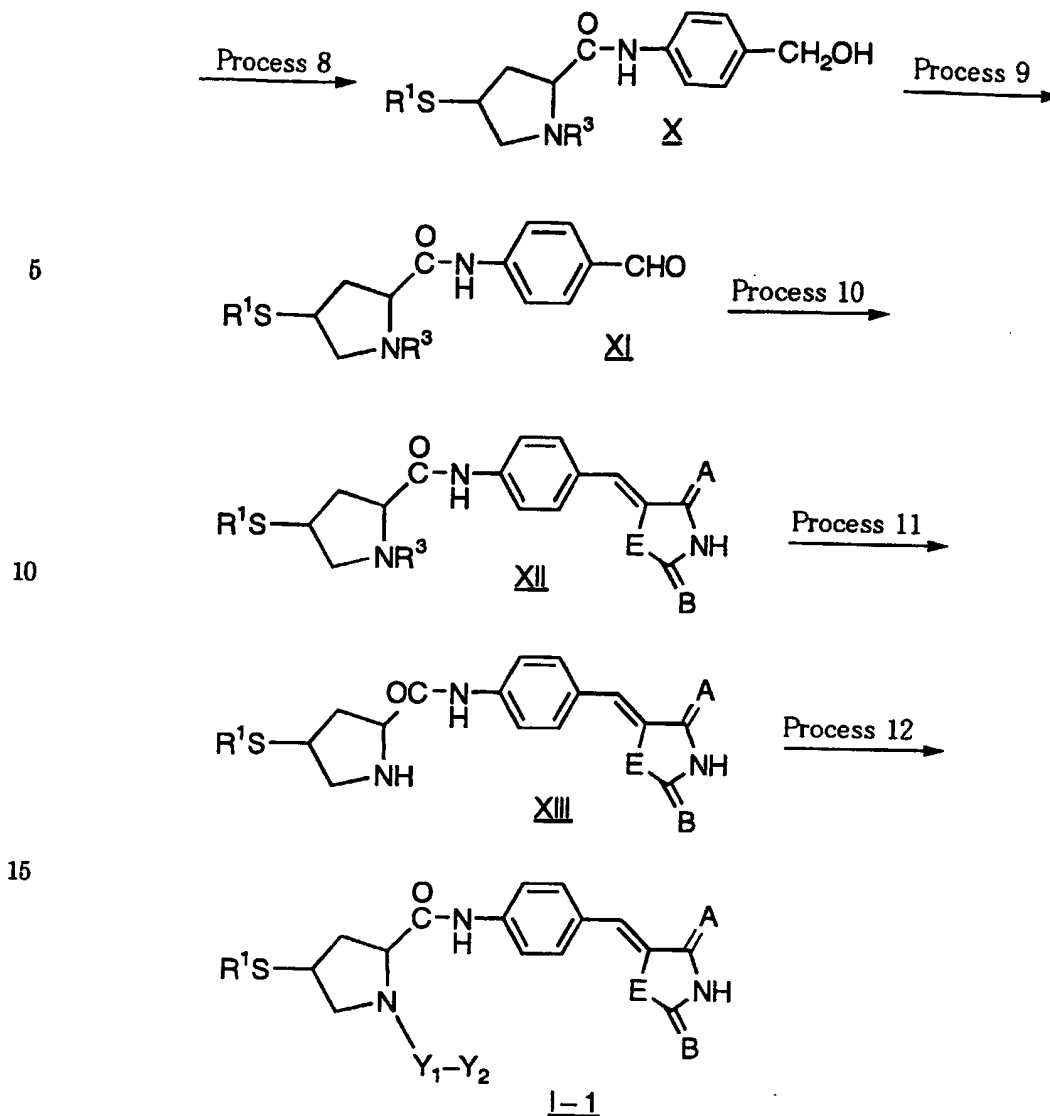
5 Method N

7) Compounds having thiazolidinedione at the 4-position of pyrrolidine ring.

The methods above will be hereinafter described in more detail.

10 <Method A>





wherein R^1 , A, B, E, Y_1 and Y_2 are as defined above and R^2 is lower alkyl such as methyl, ethyl, t-butyl, and the like, or aralkyl such as benzyl, or the like; Tr is trityl group; R^3 is N-protecting group; R^4 is hydroxy-protecting group; and W is a leaving group.

Process 1 (II \rightarrow III)

This process involves the protection of N on pyrrolidine ring, followed by conversion of 4-hydroxyl group into a leaving group. N-protecting reaction is carried out in a solvent such as tetrahydrofuran, dichloromethane, benzene, or the like, in the



presence of a base such as triethylamine, pyridine, or the like, using Boc-protecting agent such as [2-(t-butoxycarbonyloxy-imino)-2-phenylacetonitrile] (Boc-ON), t-butoxycarbonyl anhydride [(Boc)₂O], t-butoxycarbonylazide (Boc-N₃), and the like;

5 PMZ-protecting agent such as 4-methoxybenzyloxycarbonylazide, 4-methoxybenzyl S-(4,6-dimethylpyrimidine-2-yl)thiocarbonate, 4-methoxybenzyloxycarbonyloxyimino)-2-phenylacetonitrile (MOZ-ON), and the like; or PNZ-protecting agent such as p-nitrobenzylchloroformate, and the like, so as to form carbamate.

10 As the next step, hydroxyl group is converted into a leaving group. Examples of leaving group include O-mesylate, O-tosylate, O-triflate, halogen, and the like. To introduce such a leaving group, the reaction is carried out according to a conventional manner using mesyl chloride, tosyl chloride,

15 trifluoromethanesulfonyl chloride, phosphorous trichloride, phosphorous pentachloride, or the like. (Japanese Patent Publication (KOKAI) 294970/1997; USP 5317016).

Process 2 (III ->IV)

This process involves the conversion of the 4-leaving

20 group on pyrrolidine ring, which group was introduced in the Process 1 above, into sulfur-containing substituent (acetylthio). The reaction is conducted in dimethylformamide in the presence of potassium thioacetate while heating at 50-60 °C.

Process 3 (III ->V)

25 The purpose of this process is the same as that of process 2. In this process, tritylthio, instead of acetylthio, is incorporated, which is carried out by reacting with sodium tritylthio in dimethylformamide or tetrahydrofuran.



- 16 -

Processes 4 & 5 (IV ->VI and V ->VI)

In these processes, the sulfur-containing substituent is deprotected to give a sodium salt, which is then reacted with an alkyl halide (e.g., methyl iodide, 2-bromopropane), alkenyl halide (e.g., geranyl halide) or aralkyl halide (e.g., benzyl bromide) to give -S-R¹ derivative. In the process 4, a derivative having -S-R¹ at the 4-position is prepared by reacting a compound IV with sodium methylate at 0-25°C, followed by addition of a halide above.

10

In the process 5, a derivative having -S-R¹ at the 4-position is prepared by deprotecting the trityl group with silver nitrate, treating the resultant silver salt with hydrogen sulfide, converting the resultant thiol into S-sodium salt, and
15 reacting the S-sodium salt with the halide above. To effect the reaction, silver nitrate in methanol is first added and the resulting silver salts are recovered by precipitation or extraction. The silver salt in dichloromethane or tetrahydrofuran is treated with hydrogen sulfide for 1 - 3 hr at
20 a temperature range of ice-cooling to ambient temperature to give a 4-thiol, to which is added sodium methylate in a solvent such as toluene, methanol, dichloromethane, or the like. The mixture, when treated with the halide above, after concentrating to dryness to isolate S-sodium salt or as it is, gives a 4-S-R¹
25 compound.

Process 6 (VI -> VII)

In this process, an ester VI is hydrolyzed with a base such as dilute sodium hydroxide, potassium hydroxide, or the like, in
30 a solvent such as methanol, dimethyl sulfoxide, or the like.

Process 7 (VII -> IX)

In this process, an amide bond is formed using a carboxylic acid VII obtained in process 6 and an amine derivative VIII by a method such as activated ester method, acid chloride method, or mixed acid anhydride method, or the like. The amine derivative VIII used in this process can be prepared by, for example, protecting hydroxyl group of p-nitrobenzyl alcohol with t-butyltrimethylsilyl chloride, t-butylchlorodiphenylsilane, tetrahydropyran, or the like, in a solvent such as tetrahydrofuran, dimethylformamide, or the like, in the presence of imidazole, and converting the nitro group into amine group through the catalytic hydrogenation using palladium or palladium on carbon in the atmosphere of hydrogen gas.

Examples of amine derivatives include 4-(t-butyltrimethylsilyloxymethyl)aniline. The present process is carried out in a solvent such as tetrahydrofuran, dichloromethane, toluene, benzene, or the like. In the activated ester method, 1-hydroxybenzotriazole, hydroxysuccinimide, dimethylaminopyridine, or the like, is used in association with dicyclohexylcarbodiimide, 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride are used as a condensing agent. Further, in the acid chloride method, the free carboxylic acid is converted into acid chloride using an agent such as thionyl chloride or oxalyl chloride. In the mixed acid anhydride method, mixed acid anhydride is formed using ethyl chloroformate, isobutyl chloroformate, or the like. In the reaction, a base(s) such as triethylamine or pyridine can be used, if necessary.

Process 8 (IX → X)

This process involves the removal of the hydroxy-



protecting group R⁴. The deprotection is carried out using tetrabutylammonium fluoride, acetic acid, or the like, in tetrahydrofuran.

Process 9 (X -> XI)

- 5 This process involves the oxidation of alcohol to aldehyde. It is carried out by Swarn oxidation, Jones' oxidation or a method using an oxidizing agent such as pyridinium chlorochromate, pyridine-SO₂ complex, or the like.

Process 10 (XI -> XII)

- 10 This process involves the production of a benzylidene derivative XII by reacting an aldehyde XI obtained in the previous process with 2,4-thiazolidinedione, 2-thioxo-4-thiazolidinone, or 2,4-oxazolidinedione. The reaction is carried out in a solvent such as benzene, toluene, or the like, under a condition for
15 Knoevenagel reaction using acetic acid and piperidine as a catalyst for 2 to 15 hr under refluxing temperature.

Process 11 (XII -> XIII)

- This process involves the deprotection of the protected N-atom of pyrrolidine ring. A salt of the corresponding
20 acid is obtained through the reaction with, for example, 5-20 equivalents of an inorganic acid, e.g., hydrochloric acid, hydrobromic acid, for 2 to 6 hr in methanol or ethyl acetate, and the removal of the solvent in vacuo.

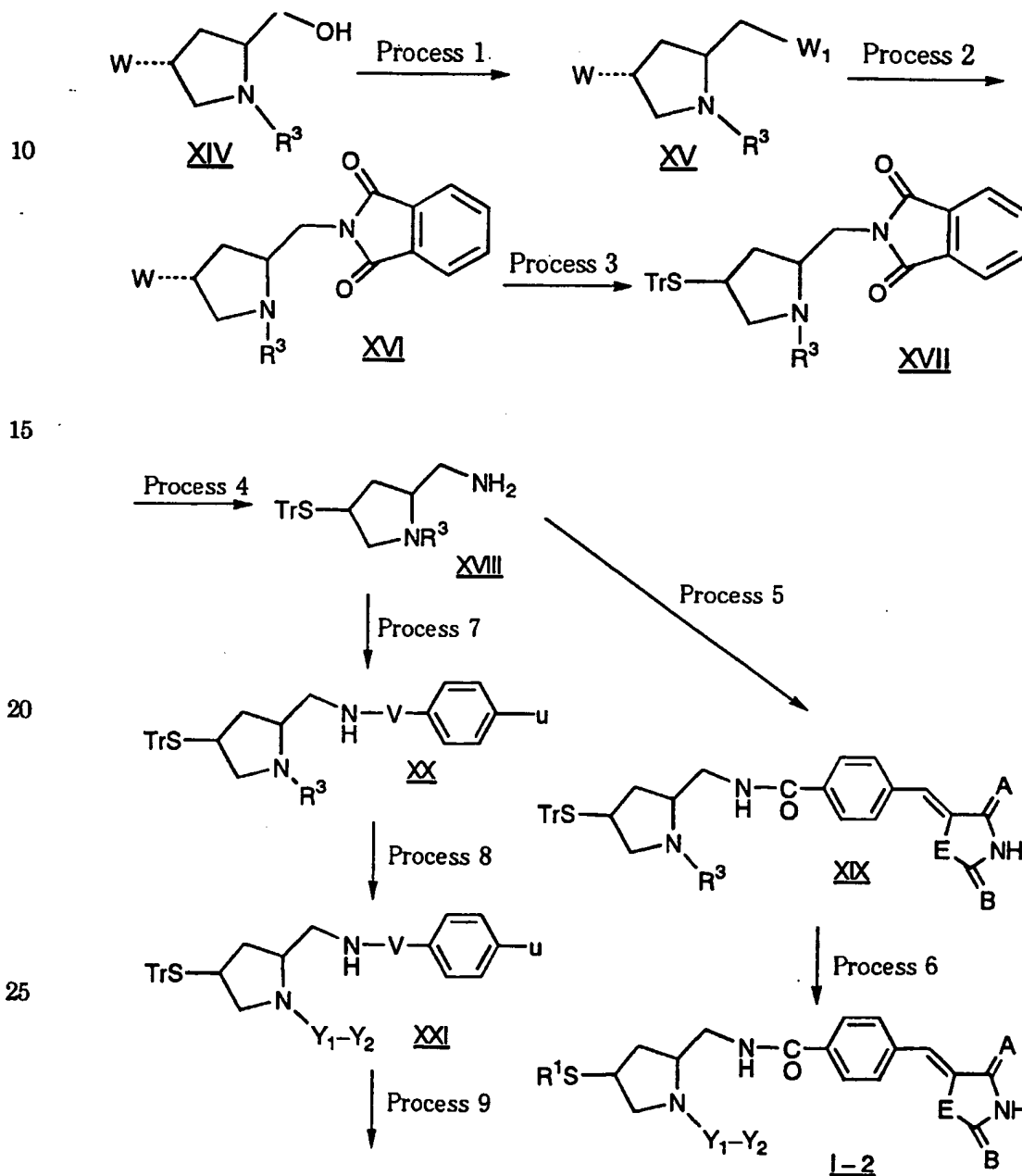
Process 12 (XIII -> I-1)

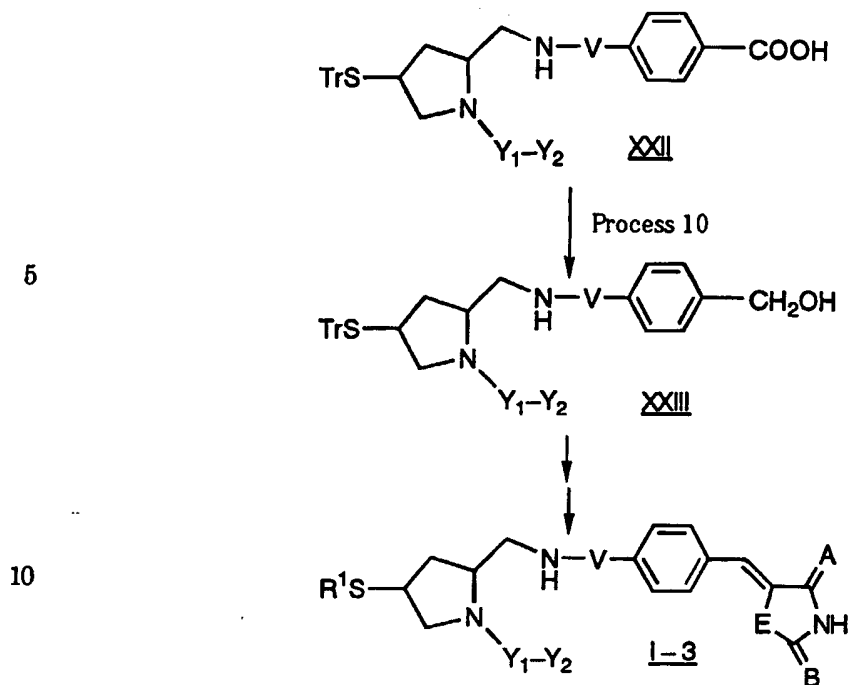
- 25 This process involves the formation of amide, sulfonamide, urea or thiourea at the N-position of pyrrolidine ring. The formation of amide bond is carried out by reacting with acyl halide in the presence of a base such as triethylamine or pyridine,



if necessary. When the acylating agent is a carboxylic acid, the reaction can be conducted in a manner similar to that described in Process 7 above. The formation of sulfonamide is carried out by reacting substituted sulfonyl chloride derivatives in the presence of a base such as triethylamine or pyridine. The formation of urea, thiourea can be carried out using isocyanates or isothiocyanates.

<Method B₁>





wherein R^1 , R^3 , A, B, E, W, Y_1 and Y_2 are as defined above and V is $-SO_2-$, $-CO-$ or $-CS-$. W_1 is a leaving group and u is a protected carboxylic acid group.

This method is related to the synthesis of amides or sulfonamides wherein the side chain at the 2-position of pyrrolidine ring is elongated with methylene.

Process 1 (XIV \rightarrow XV)

20 This process involves the conversion of the hydroxyl group in the 2-hydroxymethyl group into a leaving group. This process is, for example, carried out in a manner similar to that used for the conversion of hydroxyl group into a leaving group in the Process 1 of Method A above. The starting compound can be

25 obtained by reducing the compound obtained in process 1 of Method A.

Process 2 (XV \rightarrow XVI)

This process involves the conversion of the leaving



group at the 2-position into a phthalimide group. It is carried out by heating a compound XV with potassium phthalimide for 3 to 12 hr in a solvent such as dimethylformamide or tetrahydrofuran.

Process 3 (XVI ->XVII)

5 This process involves the conversion of the leaving group at the 4-position into a tritylthio group in a manner similar to that described in Process 3 of Method A.

Process 4 (XVII ->XVIII)

 This process is related to the Gabriel synthesis where
10 the phthalimide group at the 2-position is converted into an amine. The reaction is carried out by heating a starting compound XVII with hydrazine hydrate for several hours in a solvent such as methanol, dichloromethane, or the like.

Process 5 (XVIII ->XIX)

15 This process involves the formation of an amide bond using a benzoic acid derivative having thiazolidine ring. The reaction can be carried out in a manner similar to that described in Process 12 of Method A using 4-(4-oxo-2-thioxothiazolidin-5-ylidenemethyl)benzoic acid, 4-(2,4-dioxothiazolidin-5-ylidenemethyl)benzoic acid or 4-(2,4-dioxooxazolidin-5-ylidenemethyl)benzoic acid described in JP 05306224 or Can. J.
20 Chem., 36, 1579 (1958).

Process 6 (XIX -> I-2)

 In this process, the substituent at the 1-position
25 is converted into Y_1-Y_2 in accordance with the Processes 11 and 12 of Method A, and then the substituent at the 4-position is converted into $-SR^1$ group in accordance with the Process 5 of Method A. The order of the steps for converting the substituent at the 1- or



4-position can be reversed.

In the case of compounds I wherein X_1 is $-\text{CH}_2\text{NHSO}_2-$ or $-\text{CH}_2\text{NHCS}-$, the aimed compound I-2 can be prepared by treating the product in Process 4 in the following manner.

5 Process 7 (XVIII \rightarrow XX)

In this process, the product obtained in Process 4 is converted into an amide, thioamide or sulfonamide. A compound XVIII is reacted with a reactive derivative of benzoic acid, thiobenzoic acid or benzenesulfonic acid, which has the substituent u, in the presence of a base such as triethylamine or pyridine. To obtain an ureide or thioureide derivative, the compound XVIII can be reacted with an isocyanate or thiocyanate. The reaction generally completes in several ten minutes to 1 hr. The substituent u stands for a protected carboxyl group, and can be
10 an ester such as methyl ester, trimethylsilyl, and the like.
15

Process 8 (XX \rightarrow XXI)

This process can be carried out in a manner similar to those described in Processes 11 and 12 of Method A.

Process 9 (XXI \rightarrow XXII)

20 This process is related to hydrolysis and can be carried out in a manner similar to that described in Process 6 of Method A.

Process 10 (XXII \rightarrow XXIII \rightarrow I-3)

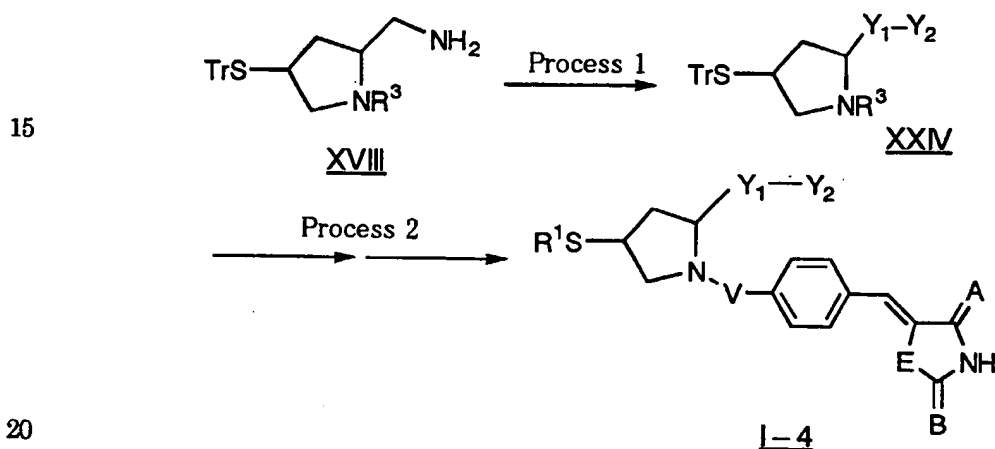
In this process, the carboxylic acid moiety is first
25 converted into a mixed acid anhydride, followed by reduction to hydroxymethyl. Thus, a mixed acid anhydride of XXII is formed using ethyl chloroformate or isobutyl chloroformate in a solvent such as tetrahydrofuran, dioxane, or the like, using a base such



as triethylamine, pyridine, or the like under ice-cooling or at room temperature. The so formed mixed acid anhydride is then reduced in aqueous solution of sodium borohydride.

A compound XXIII produced in Process 10 is converted into a benzylidene in a manner similar to that described in Method A, Process 9 and processes thereafter. The product is then treated in a manner similar to that described in Process 5 of Method A to introduce $-S-R^1$ group at the 4-position to yield the aimed compound I-3. The order of step for producing benzylidene and that for or introducing $-S-R^1$ group can be reversed.

<Method B₂>



wherein R^1 , R^3 , A, B, E, V, Y_1 and Y_2 are as defined above. Y_1 is $-CH_2NHCO-$ or $-CH_2NHSO_2-$.

This method is related to the synthesis of compounds having benzylidene at the 1-position of pyrrolidine ring.

25 Process 1 (XVIII \rightarrow XXIV)

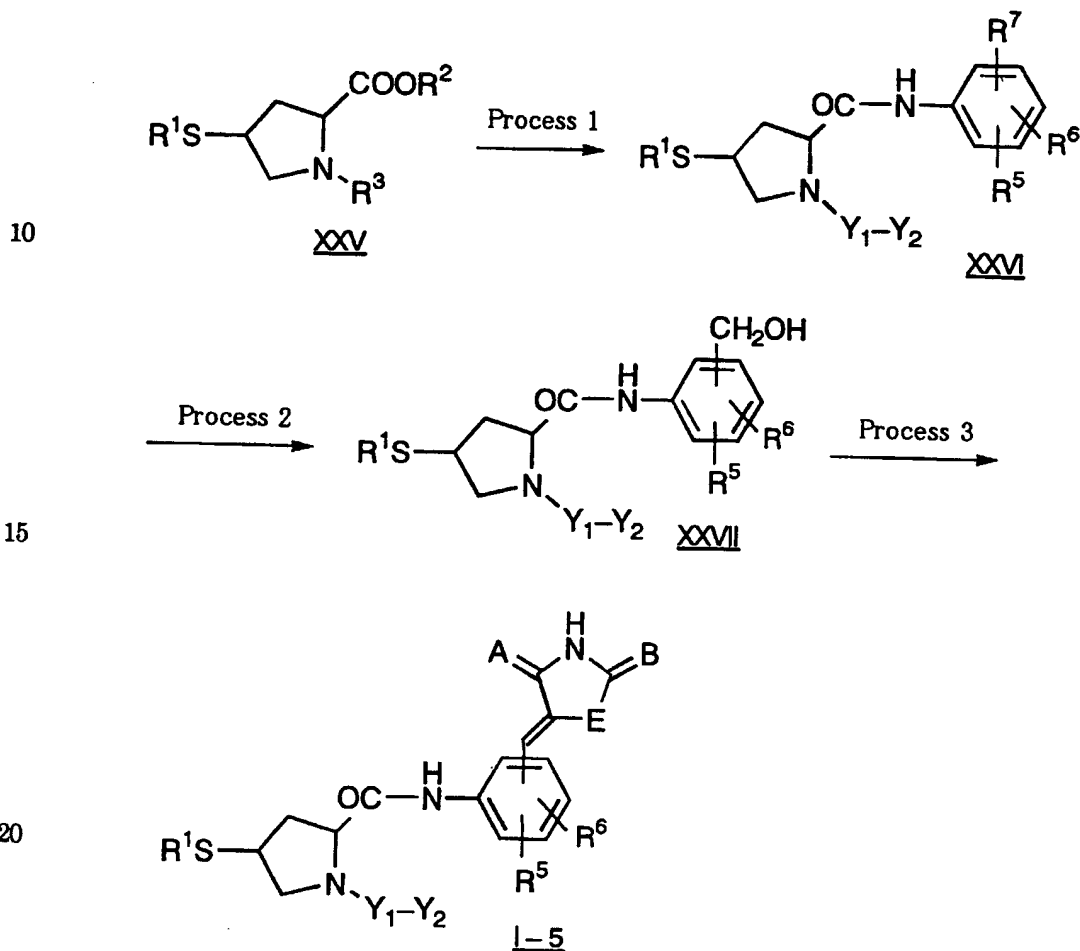
In this process, a compound XVIII prepared in Process 4 of Method B₁ is converted into an amide or sulfonamide in a manner similar to that of Process 12 of Method A.



Process 2 (XXIV -> 1-4)

This process can be effected in a manner similar to those of Process 5 of Method A and Process 8 of Method B₁.

5 <Method C>



wherein R¹, R², R³, A, B, E, Y₁ and Y₂ are as defined above, R⁷ is t-butyldimethylsilyloxymethyl, carboxy, ester, or the like, R⁵ and R⁶ each are independently hydrogen, t-butyloxycarbonylamino, alkyl, alkoxy, halogen, or the like.

This method is related to the synthesis of benzylidene derivatives which are different in the binding sites, and have



substituents.

Process 1 (XXV ->XXVI)

This process involves the formation of an amide bond.

A compound XXV is treated in a manner similar to those described
 5 in Processes 6 and 7 of Method A in this order. In addition, R'¹
 at the N-position is replaced with Y₁-Y₂ in a manner similar to those
 described in Processes 11 and 12 of Method A. The order of the
 step for amide-formation and that for Y₁-Y₂-substitution may be
 selected depending on the characteristics of the compound.

10 Process 2 (XXVI -> XXVII)

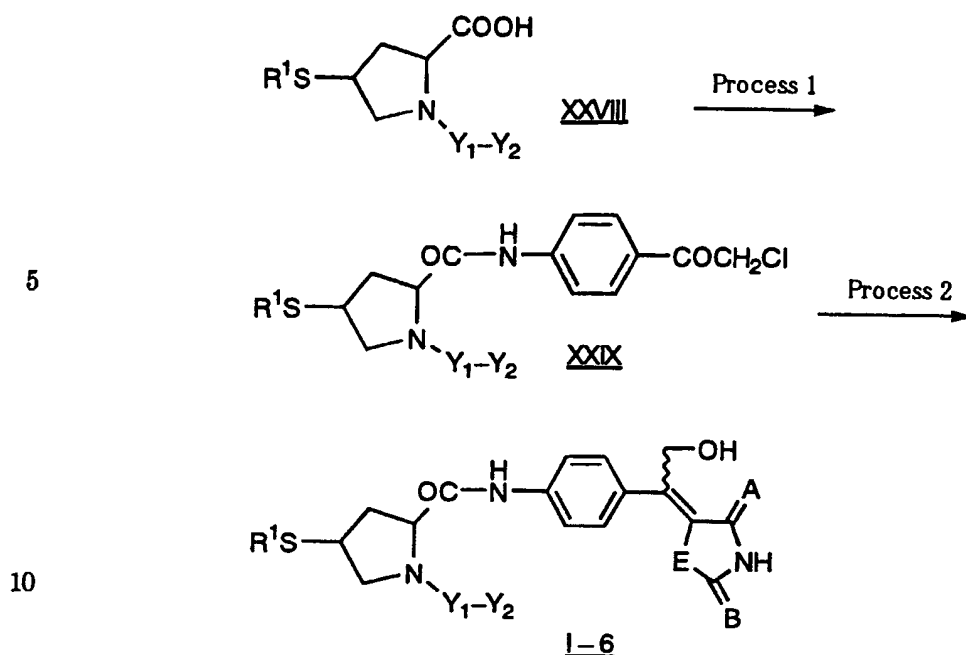
This process involves the preparation of
 hydroxymethyl-substituted benzene derivatives. The conversion
 into hydroxymethyl can be carried out, when R' is t-butyl
 dimethylsilyloxymethyl group, in accordance with the method
 15 described in Process 8 of Method A, and, when R' is methyl ester,
 through the reduction with lithium hydride. In the case of other
 ester groups, the conversion can be carried out as described in
 Processes 9 and 10 of Method B.

Process 3 (XXVII -> I-5)

20 The product of Process 2, when treated in a manner
 similar to that described in Method A, gives the aimed compound
 I-5.

<Method D>





wherein R^1 , A, B, E, Y_1 and Y_2 are as defined above.

This method is related to the synthesis of benzylidene derivatives having hydroxymethyl group on the double bond in the benzyl portion. The synthesis of p-chloroacetylaniline or
 15 formation of benzylidene can be effected in accordance with the method described in a literature such as Arie Zask et al., Tet. Lett., 34, 2719, 1993.

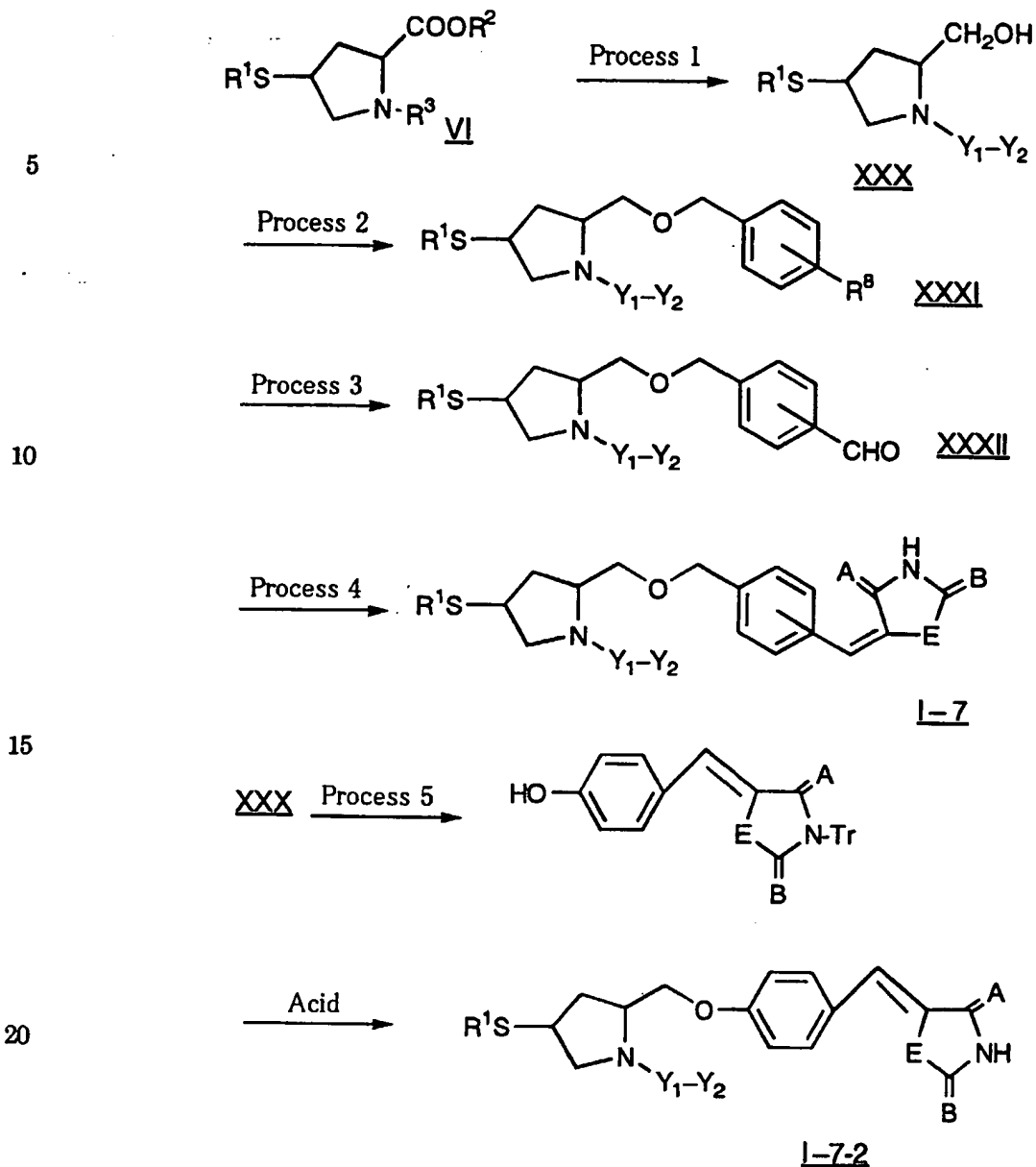
Process 1 (XXVIII \rightarrow XXIX)

20 This process involves the formation of an amide bond by reacting a compound XXVIII with p-chloroacetylaniline prepared by the method described in the literature above in a manner similar to that described in Process 7 of Method A.

Process 2 (XXIX \rightarrow I-6)

25 In this process, 2,4-thiazolidinedione is first converted into anion with n-butyllithium in tetrahydrofuran, and then allowed to react with chloroacetyl compound.



<Method E₁>

wherein R¹, R², R³, A, B, E, Y₁ and Y₂ are as defined above and R⁸ is cyano, ester, carboxy or hydroxymethyl.

25

This method is related to the synthesis of compounds wherein the benzylidene portion and pyrrolidine portion are linked via an ether bond.

Process 1 (VI → XXX)



This process is related to the reduction of ester to give hydroxymethyl group. The reduction is carried out using a reducing agent such as lithium aluminium hydride, lithium borohydride, or the like, in a solvent such as tetrahydrofuran, which is followed by the procedures described in Process 8 of Method B₁.

Process 2 (XXX ->XXXI)

This process is related to the formation of an ether bond. The compound XXX is treated with sodium hydride in tetrahydrofuran, dimethylformamide, or the like, and reacted with a benzyl halide derivative, e.g., α -bromo-p-tolunitrile, about overnight at a temperature from -70 °C to ambient temperature to give the compound XXXI.

Process 3 (XXXI ->XXXII)

In this process, the substituent R⁸ on benzene ring is converted into aldehyde through hydrolysis, esterification, reduction, oxidation, or the like. For example, when R⁸ is cyano, it is carried out by reacting a starting compound XXXI with diisobutylaluminium hydride in a solvent such as benzene, toluene, or the like, about overnight at a temperature from 0 °C to ambient temperature optionally under heating at about 50 °C.

Process 4 (XXXII -> I-7)

This process is related to the formation of benzylidene bond through the Aldol condensation in a manner similar to that described in Process 10 of Method A. The product, when treated conventionally, gives the aimed compound I-7.

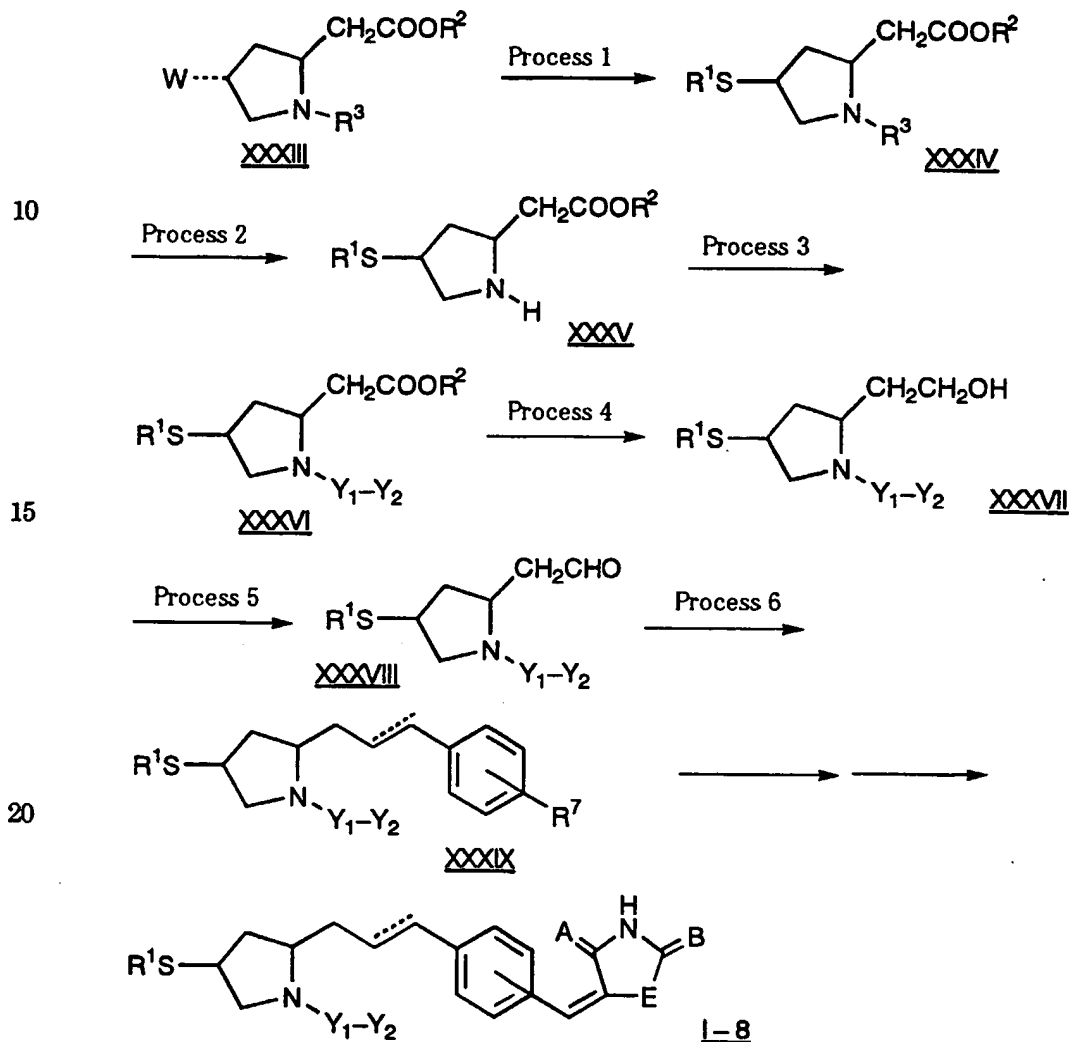
Process 5 (XXX ->I-7-2)

In this process, the compound I-7-2 is prepared by



subjecting a starting compound XXX to Mitsunobu reaction to form phenyl ether bond, and deprotecting the trityl group on nitrogen atom on thiazolidine or oxazolidine ring by treatment with acid such as trifluoroacetic acid, or the like.

5 <Method E₂>



wherein R^1 , R^2 , R^3 , R^7 , A, B, E, W, Y_1 and Y_2 are as defined above.

This method is related to the synthesis of compounds wherein the pyrrolidine and benzylidene portions are linked via carbon-carbon bond including double bond.



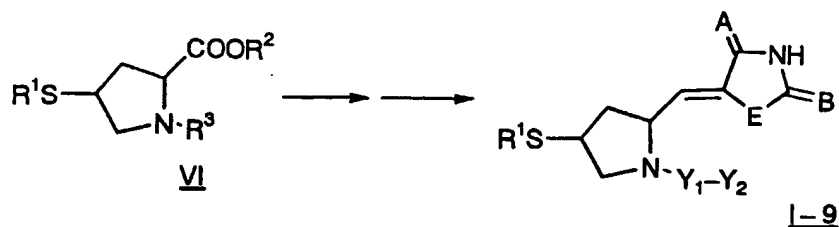
Processes 1 - 5 (XXXIII ->XXXVIII)

The starting compound XXXIII is prepared following the teaching of M. Sunagawa et al., Journal of Antibiotics, 44(4), 459 (1991). Processes 1-5 leading to an aldehyde can be effected in 5 manners similar to those described in Method A.

Process 6 (XXXVIII -> I-8)

In this process, the formation of benzylidene and the catalytic hydrogenation are carried out simultaneously or optionally in series to give a saturated bond(s). For example, 10 when R^7 is an ester, a starting compound XXXVIII is first heated to reflux with, for example, methyl 4-(bromotriphenylphosphonium-methyl)benzoate, in a solvent such as ethanol or methanol in the presence of a base such as triethylamine for about 14 hr to yield the aimed benzylidene compound (I-8). The 15 catalytic hydrogenation of a double bond(s) is carried out in a solvent such as methanol or ethyl acetate using platinum as a catalyst in an atmosphere of hydrogen. The resultant product, when treated in the same manner as that described in Method E₁, gives the aimed compound.

20 <Method F> (VI ->I-9)



25

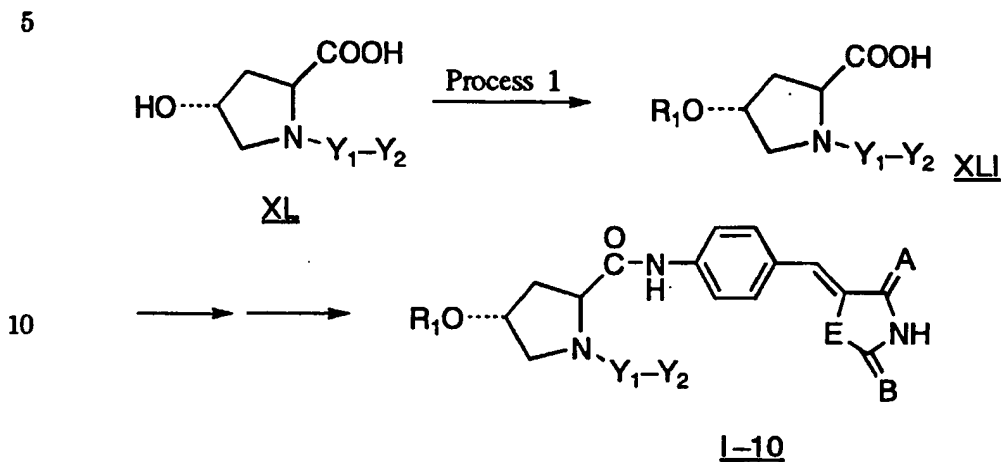
wherein R^1 , R^2 , R^3 , A, B, E, Y_1 and Y_2 are as defined above.

This method is related to the synthesis of compounds having thiazolidine or oxazolidine ring linked to pyrrolidine ring



at the 2-position via methyldene. The conversion of respective substituent can be carried out in manners similar to those described in Method A.

<Method G> (XL -> XLI -> I-10)



wherein R^1 , R^3 , A, B, E, Y_1 and Y_2 are as defined above.

This method is related to the synthesis of compounds having oxygen atom at the 4-position of pyrrolidine ring.

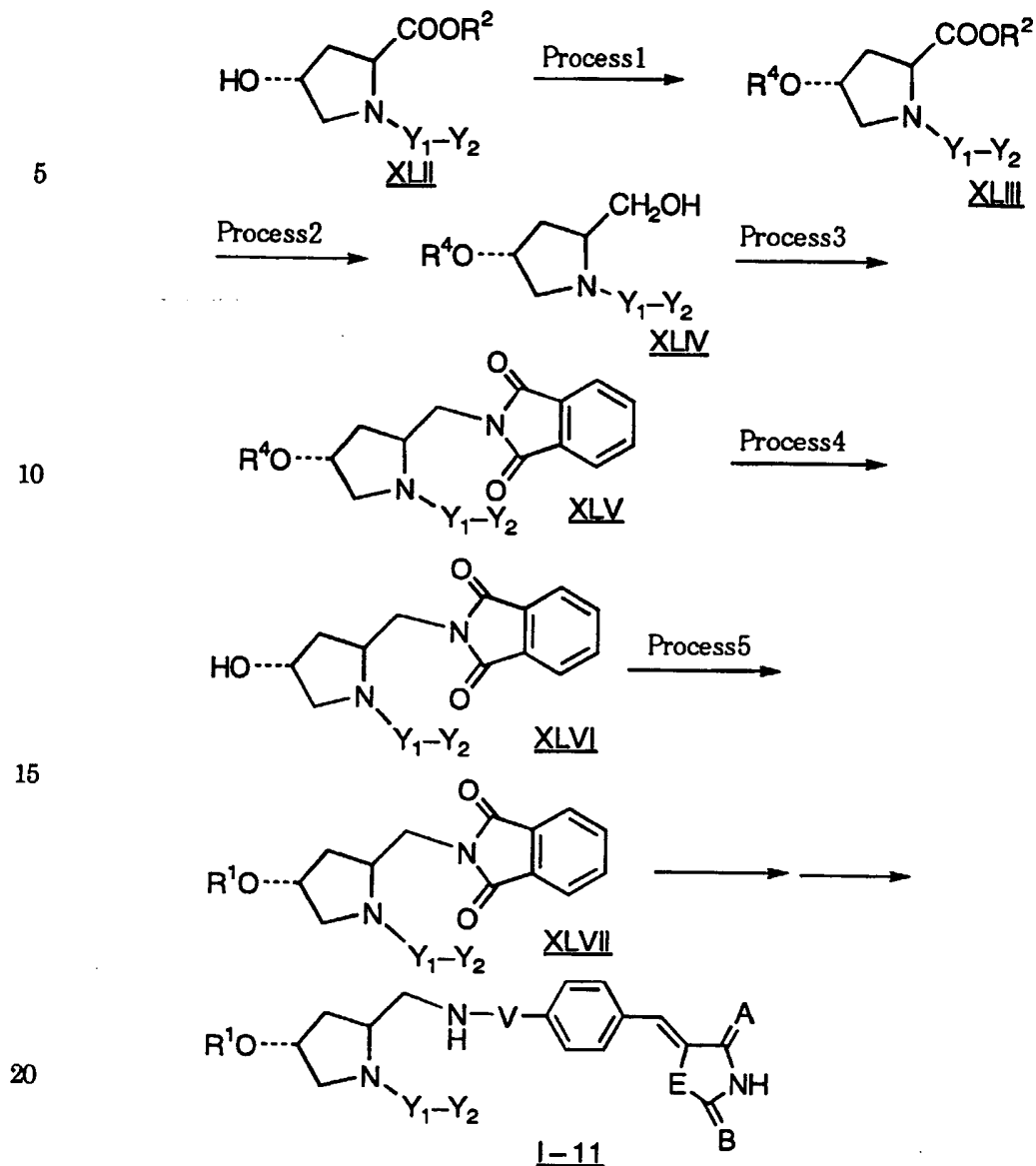
Process 1

This process is related to the formation of an ether bond in a 4-hydroxy compound derived from the starting compound used in the Method A. To the 4-hydroxy compound is added a strong base such as sodium hydride in a solvent, e.g., dimethylformamide, in the presence of alkyl halide. The reaction completes in 3 to 15 hours at a temperature range of 0 °C to ambient temperature.

The rest of the processes following the Process 1 above, involving the conversion of respective substituent, can be carried out in manners similar to those described in Method A.



<Method H>

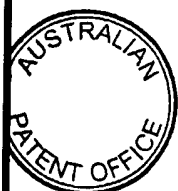


wherein R¹, R², R⁴, A, B, E, V, Y₁ and Y₂ are as defined above.

This method is related to the synthesis of compounds
 25 having oxygen atom linked at the 4-position of pyrrolidine ring and
 an amide formed by elongating the 2-side chain with methylene.

Process 1 (XLII → XLIII)

This process is related to the protection of hydroxyl



group. For example, derivatives having a tetrahydropyranyl-protected hydroxyl group can be prepared through the treatment with 3,4-dihydro-2H-pyran in dichloromethane in the presence of p-toluenesulfonic acid as a catalyst.

5 Process 2 (XLIII -> XLIV)

This process is the same as Process 1 of Method E₁, which is related to the conversion of ester into hydroxyl group.

Process 3 (XLIV -> XLV)

This process is related to the conversion of hydroxyl
10 group into phthalimide group by means of Mitsunobu reaction. For example, after reacting triphenylphosphine and diisopropyl azodicarboxylate or diethyl azodicarboxylate in tetrahydrofuran at low temperature, phthalimide and a compound XLIV are added in series thereto and the mixture is reacted for several hours at a
15 temperature range of ice-cooling to ambient temperature for about overnight.

Process 4 (XLV -> XLVI)

This process is related to the deprotection of protected hydroxyl group through the reaction with p-
20 toluenesulfonic acid or aqueous acetic acid in a solvent such as methanol, tetrahydrofuran, or the like, at room temperature about overnight.

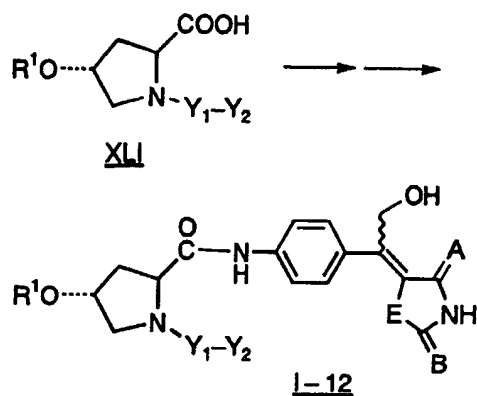
Process 5 (XLVI -> I-11)

This process is the same as the Process 1 of Method
25 G and is related to the formation of an ether bond.

The resultant compound is then treated in manners similar to those described in Processes 4 and 5 of Method B to give the aimed compound.



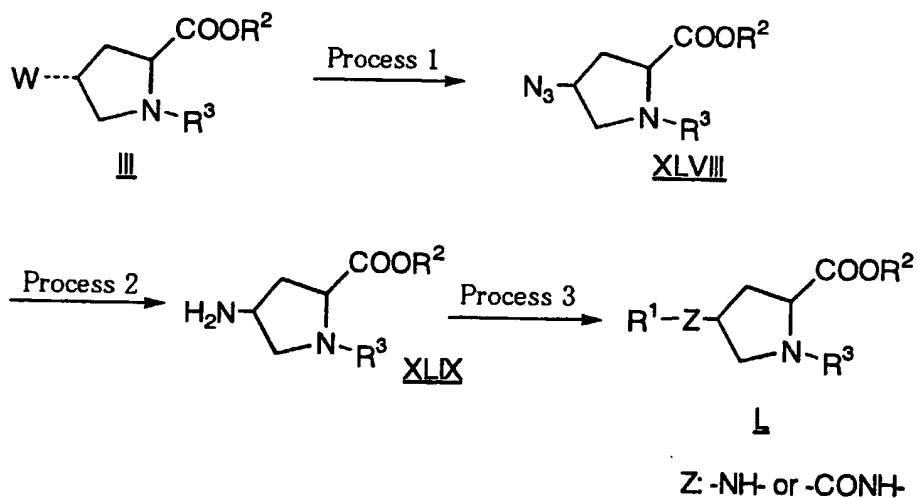
<Method I>



wherein R^1 , A, B, E, Y_1 and Y_2 are as defined above.

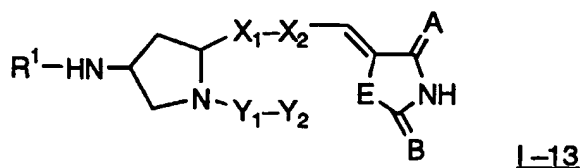
This method is related to the synthesis of compounds having an oxygen atom at the 4-position of pyrrolidine ring and hydroxymethyl group on the double bond in the benzyl portion. This method can be effected in a manner similar to that described in Method D using a carboxylic acid obtained in Method G as a starting compound.

<Method J>





5



wherein R^1 , R^2 , R^3 , X_1 , X_2 , A , B , E , W , Y_1 and Y_2 are as defined above.

10

This method is related to the synthesis of compounds having a nitrogen atom at the 4-position of pyrrolidine ring.

Process 1 (III -> XLVIII)

In this process, a nitrogen atom is introduced at the 4-position through the reaction with sodium azide in a solvent such as dimethylformamide at 40 to 60 °C for about 2 to 9 hr.

15

Process 2 (XLVIII -> XLIX)

In this process, an azide group is reduced to amine through the catalytic hydrogenation with platinum in a solvent such as dioxane in the atmosphere of hydrogen gas.

20

Process 3 (XLIX -> L)

This process is related to the alkylation, which is carried out through the reaction with an alkyl halide in the presence of a base such as potassium carbonate or sodium hydroxide in acetonitrile for about 16 hr at a temperature of ice-cooling to room temperature.

25

Process 4 (L -> I-13)

This process is related to the protection of an amine when Z is NH . When Z is $-CONH-$, the objective compound I-13 can

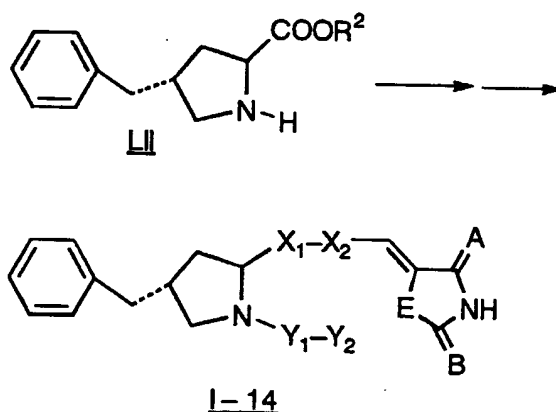


b prepared directly from a compound L without obtaining an intermediate LI. This process can be carried out by the method described in the Process 1 of Method A.

The resultant compound, when treated in manners similar to those described above, gives the aimed compound.

<Method K> (LII -> I-14)

10



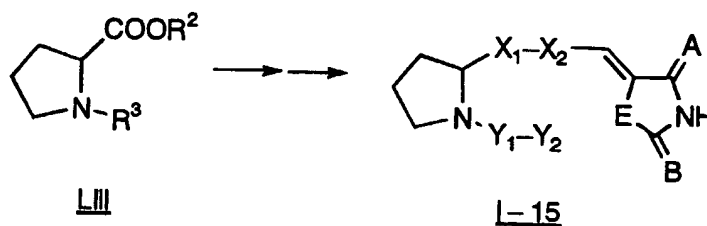
15 wherein R^2 , A, B, E, X_1 , X_2 , Y_1 and Y_2 are as defined above.

This method is related to the synthesis of compounds having substituent on the carbon atom at the 4-position. Pyrrolidines having a carbon atom at the 4-position can be synthesized in accordance with the method described in a literature (J. Org. Chem., 57, 1927, 1992). The conversion at the 1- and 2-positions can be carried out in a conventional manner.

20

<Method L> (LIII -> I-15)

25

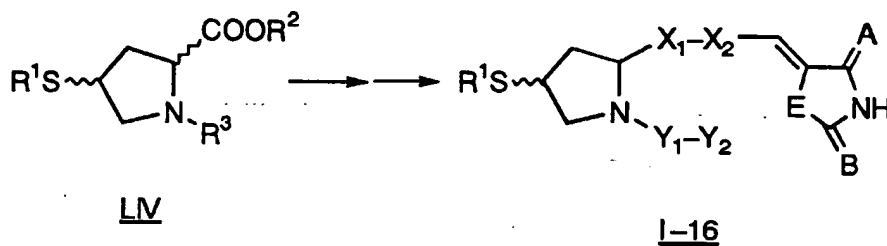


wherein R^2 , R^3 , A, B, E, X_1 , X_2 , Y_1 and Y_2 are as defined above.



This method is related to the synthesis of compounds having no substituent at the 4-position. The aimed compounds can be prepared in a manner similar to that described above except that proline is used as a starting compound.

5 <Method M> (LIV → I-16)



wherein R¹, R², R³, A, B, E, X₁, X₂, Y₁ and Y₂ are as defined above.

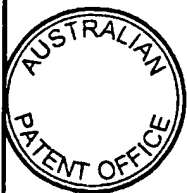
This method is related to the synthesis of compounds which correspond to those described in Methods A and B₁, but are in different configuration(s) at the 2- and/or 4-position.

- 15 Compounds having sulfur atom at the 4-position obtained in the above are in (2β, 4β) configuration though, those prepared by Method M are in (2β, 4α), (2α, 4β), or (2α, 4α) configuration.

All the starting compounds are known in Japanese Patent Publication (KOKAI) No. 294970/1993 (USP 5317016). The conversion of respective functional group can be carried out in a manner similar to that described above. Compounds having substituents in other positions are obtainable according to reactions similar to those mentioned above. When a compound contains a functional group(s) possibly interfering the reaction, it can be protected and deprotected at an appropriate stage.

20
25

The present invention is not restricted to any particular isomers but includes all possible isomers and racemic modifications.



The compound I of the present invention has an activity of inhibiting the production of prostaglandin E, through the inhibition of cPLA₂ activity and is expected to be useful in the prevention or treatment of diseases attributable to
5 prostaglandin or leukotriene.

When using a compound I of the present invention in the treatment, it can be formulated into ordinary formulations for oral or parenteral administration such as intravenous injection and percutaneous administration. That is, the compound of the present
10 invention can be formulated in the form for oral administration such as tablets, capsules, granules, powders, syrup, and the like; or parenteral administration such as injectable solution or suspension for intravenous, intramuscular or subcutaneous injection, suppositories, or percutaneous formulations such as
15 ointment.

The formulations above can be prepared using appropriate carriers, excipients, solvents, and bases known to one of ordinary skill in the art. For example, tablets can be prepared by compressing or formulating an active ingredient together
20 with auxiliary components. Examples of usable auxiliary components include pharmaceutically acceptable excipients such as binders (e.g., cornstarch), fillers (e.g., lactose, microcrystalline cellulose), disintegrants (e.g., sodium glycolate starch) or lubricants (e.g., magnesium stearate).
25 Tablets may be coated appropriately. In the case of liquid formulations such as syrups, solutions, or suspensions, they may contain suspending agents (e.g., methyl cellulose), emulsifiers (e.g., lecithin), preservatives, and the like. In the case of

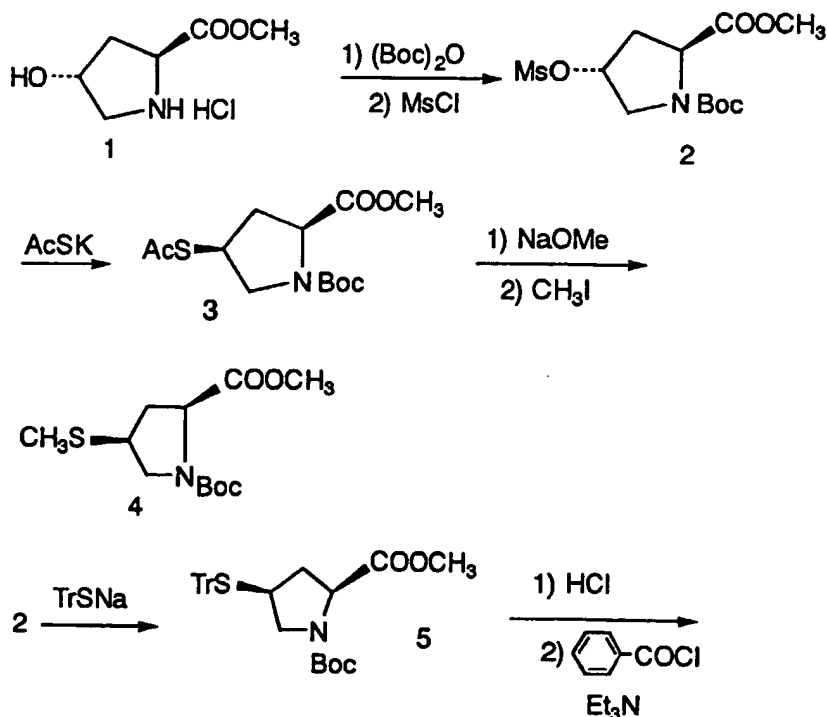


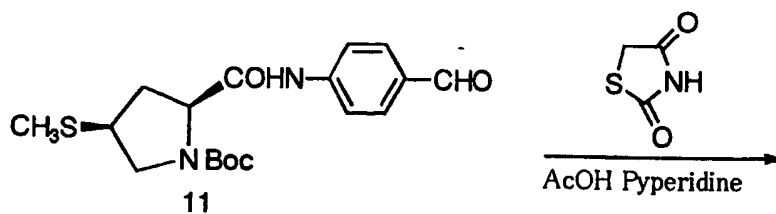
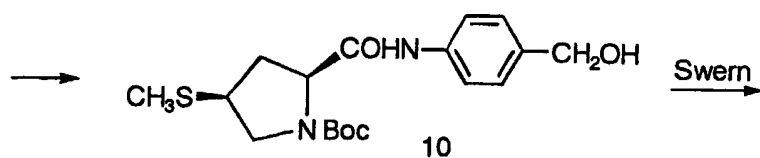
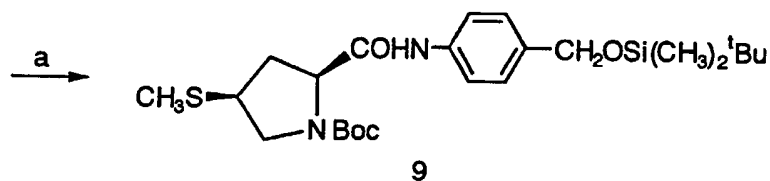
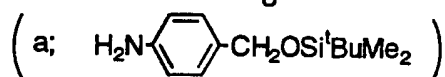
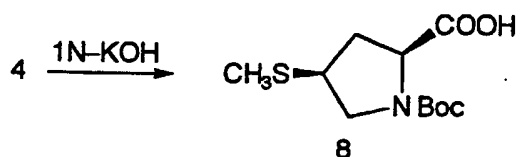
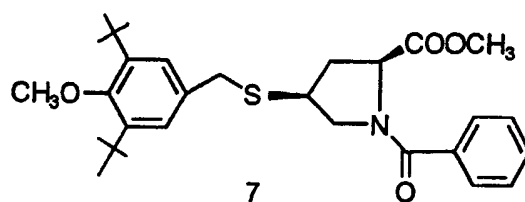
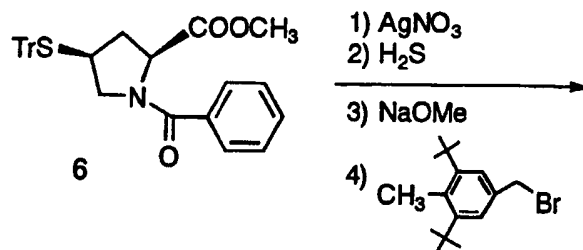
injectable formulations, it may be in the form of solution or suspension, or oily or aqueous emulsion, which may contain suspension-stabilizing agent or dispensing agent, and the like.

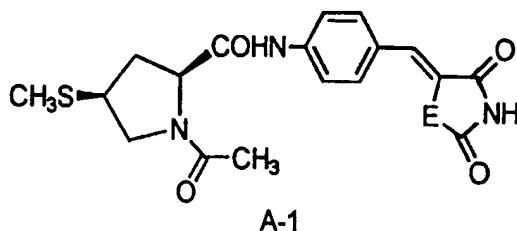
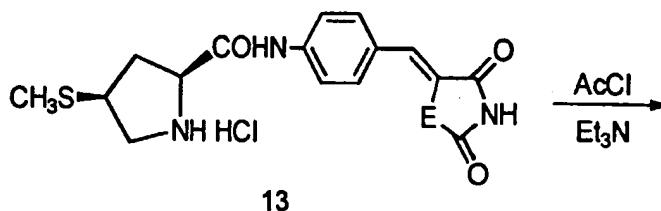
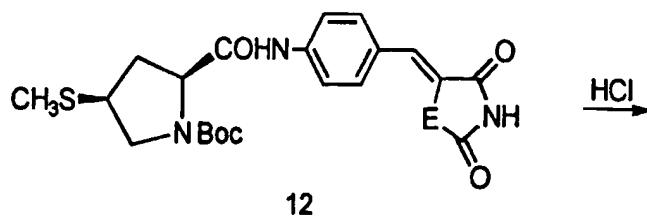
An appropriate dosage of the compound I varies depending on the administration route, age, body weight, sex, or conditions of the patient, the kind of drug(s) used together, if any, and should be determined by a physician in the end. However, in the case of oral administration, the daily dosage can generally be between about 10 - 100 mg/kg body weight. In the case of parenteral administration, the daily dosage can generally be between about 0.1 - 10 mg, preferably about 1 - 5 mg. The daily dosage can be administered in one to several divisions.

The following Examples are provided to further illustrate the present invention and are not to be construed as limiting the scope thereof.

Example 1 (Method A)







(1) 1 → 2

To a solution of 4-hydroxy-L-proline methyl ester hydrochloride (45.4 g, 250 mmol) in methylene chloride (450 ml) were added triethylamine (70ml, 2 x 250 mmol), and then di-t-butyl dicarbonate (69ml, 1.2x 250 mmol) under ice cooling. After stirring for 2 hr at room temperature, the reaction solution was washed with 2N HCl, 5% NaHCO₃, H₂O successively, dried over Na₂SO₄ and concentrated in vacuo to obtain an aimed product (72.6 g) as an oil.

The product was dissolved in methylene chloride (300 ml). To the solution were added triethylamine (38.3ml, 1.1x250 mmol) and methanesulfonyl chloride (19.4ml, 250 mmol) under ice-cooling, and the mixture stirred for 30 min at the same temperature. The reaction solution was washed with 2N-HCl, 5%



NaHCO₃ and H₂O, successively, dried over Na₂SO₄, concentrated in vacuo and recrystallized from ethyl ether/hexane to obtain mesylate (69.5 g). Yield 86%.

(2) 2 → 3

5 To a solution of mesylate (5.0 g, 15.46 mmol) in dimethylformamide (15 ml) was added potassium thioacetate (2.12 g, 1.2 x 15.46 mmol) and heated at 60 °C for 90 min. After pouring into water, the mixture was extracted with ethyl acetate. The extract was washed with H₂O, dried over Na₂SO₄, and concentrated
10 in vacuo. The residue was subjected to silica gel column chromatography and the fractions eluting with hexane/ethyl acetate (3:1) were collected to yield acetate (3.18 g) as an oil. Yield 67.8%.

Elemental analysis (C₁₃H₂₁NO₅S)

15 Calcd.: C, 51.47; H, 6.98; N, 4.62; S, 10.57

Found : C, 51.24; H, 6.95; N, 4.64; S, 10.54.

IR (CHCl₃): 1752, 1695.

(3) 3 → 4

To a solution of thioacetate (22.38 g, 73.7 mmol) in
20 toluene (74ml) was added 1M-NaOMe/MeOH (74ml, 73.7 mmol) over 8 min at -25°C. After standing for 5 min at the same temperature, iodomethane (9.2ml, 2 x 73.7 mmol) was added thereto and the mixture stirred for another 1 hr at room temperature. The reaction mixture was poured into water and extracted with ethyl acetate. The
25 extract was washed with 2N HCl, 5% NaHCO₃ and H₂O, successively, dried over Na₂SO₄, and concentrated in vacuo. The residue was subjected to silica gel column chromatography and the fractions eluting with hexane/ethyl acetate (3:1) were collected to yield



methylthio compound (20.3 g) as an oil. Yield 100%.

Elemental analysis ($C_{12}H_{21}NO_4S$)

Calcd.: C, 52.34; H, 7.69; N, 5.09; S, 11.64

Found : C, 52.14; H, 7.61; N, 5.11; S, 11.57.

5 IR ($CHCl_3$): 1752,1695.

(4) 2→5

To a suspension of 60% sodium hydride (2.9 g, 1.3 x 55.67 mmol) in tetrahydrofuran (50 ml) was added a solution of triphenylmethylmercaptane (21.5 g, 1.4 x 55.67 mmol) in
10 tetrahydrofuran (10 ml) over 15 min in an atmosphere of argon under ice-cooling. The mixture was stirred for 10 min at the same temperature.

A solution of a starting compound (18 g, 55.67 mmol) in tetrahydrofuran (60ml) was stirred in an atmosphere of argon
15 under ice-cooling. To the solution was added the previously prepared solution and the mixture stirred for 24 hr at room temperature. The reaction solution was poured into water and extracted with ethyl acetate. The extract was washed with water and concentrated in vacuo. The residue was subjected to silica
20 gel column chromatography. The fractions eluting with hexane/ethyl acetate (4:1 to 1:1) were collected and recrystallized from dichloromethane/hexane to obtain the objective compound (22.4 g). mp. 163 - 164°C, yield 80%.

Elemental analysis ($C_{30}H_{33}NO_4S$)

25 Calcd.: C, 71.54; H, 6.60; N, 2.78; S, 6.37

Found : C, 71.58; H, 6.66; N, 2.83; S, 6.30.

IR ($CHCl_3$): 1749,1690,1596,1489,1446.

NMR ($CDCl_3$): 1.34 (s, 9/2H), 1.39 (s, 9/2H), 1.66 (m, 1H), 1.85



(m, 1/2H), 2.20 (m, 1/2H), 2.66-2.95 (m, 2H), 3.17 (m, 1/2H), 3.47 (m, 1/2H), 3.68 (s, 3/2H), 3.70 (s, 3/2H), 3.98 (m, 1H), 7.18-7.50 (m, 15H).

(5) 5 → 6

- 5 Hydrogen chloride gas (31 g, 17 equivalent) was bubbled into a solution containing a starting compound (25.5 g, 50.6 mmol) in a mixture of dried methanol (300 ml) and dried dichloromethane (150 ml) under ice-cooling. After stirring for 2 hr at room temperature, the mixture was concentrated in vacuo.
- 10 The residue was flushed with toluene (x2) to obtain hydrochloride, which was dissolved in dichloromethane (150 ml). To the solution were added triethylamine (21.3ml, 3 x 50.6 mmol) and then benzoyl chloride (6.5ml, 1.1 x 50.6 mmol) under ice-cooling and a nitrogen atmosphere. After stirring for 1 hr at room temperature, the
- 15 reaction solution was washed with 2N-HCl, 5% NaHCO₃ and H₂O, successively, dried over Na₂SO₄, and concentrated in vacuo. The residue was subjected to silica gel column chromatography and the fractions eluting with hexane/ethyl acetate (2:1) were collected to yield the objective product as a foam quantitatively.
- 20 NMR (CDCl₃): 1.85 (m, 1H), 2.28 (m, 1H), 2.52 (m, 1H), 2.75 (m, 1H), 3.03 (t, J=10.8Hz, 1H), 3.74 (s, 3H), 4.47 (d. d, J=10.0, 7.8Hz, 1H), 7.00-7.52 (m, 20H).
- (6) 6 → 7

- To a solution of a starting compound (26 g, 51.2 mmol)
- 25 in methanol (300 ml) was added pyridine (10.4ml, 5 x 51.2 mmol) under ice-cooling. Silver nitrate (20 g, 2.3 x 51.2 mmol) in a mixture of methanol (40 ml) and water (40 ml) was then added to the solution over 10 min, followed by stirring for another 10 min.



After addition of water, the reaction mixture was extracted with dichloromethane (500 ml). The extract was washed with water, and dried over Na_2SO_4 to obtain a solution of silver salt in dichloromethane, which was used in the next step as it is.

5 Hydrogen sulfide was bubbled into the solution with stirring and under ice-cooling over 10 min. The precipitated silver sulfide was filtered off and the filtrate was concentrated in vacuo. The residue was subjected to silica gel column chromatography and the fractions eluting with hexane/ethyl acetate
10 (2:1) were collected to yield the thiol compound (13.13 g) as a gum.

NMR (CDCl_3): 1.74 (d, $J=7.5\text{Hz}$, 1H), 1.97 (m, 1H), 2.83 (m, 1H), 3.25 (m, 1H), 3.57 (t, $J=10.0\text{Hz}$, 1H), 3.79 (s, 3H), 3.90 (m, 1H), 4.72 (d, d, $J=9.2, 8.0\text{Hz}$, 1H), 7.34-7.62 (m, 5H).

15 A solution of the resultant thiol compound (13.13 g, 49.5 mmol) in dimethylformamide (130 ml) was stirred under cooling at -50°C under argon. To the mixture was added 2.55M/L sodium methylate/methanol solution (18.4ml, 0.95×49.5 mmol) over 1 min. Three-minute later, a solution of 3,5-di-*t*-butyl-4-methoxybenzyl
20 bromide (19.6 g, 1.2×49.5 mmol) in dimethylformamide (20 ml) was added over 7 min. The mixture was stirred for another 20 min, poured into water and extracted with dichloromethane. The extract was washed with water, dried over Na_2SO_4 , and concentrated in vacuo. The residue was subjected to silica gel column chromatography and
25 the fractions eluting with hexane/ethyl acetate (2:1) were collected to yield an aimed product (12.97 g) as a gum. Yield, 51%. A portion was lyophilized from benzene and subjected to elemental analysis.



Elemental analysis ($C_{22}H_{39}NO_4S \cdot 0.4C_6H_6$)

Calcd.: C, 71.30; H, 7.88; N, 2.65; S, 6.06

Found : C, 71.22; H, 7.92; N, 2.77; S, 5.81.

IR ($CHCl_3$): 1749, 1632, 1603, 1578, 1413.

5 NMR ($CDCl_3$): 1.35 (s, 18H), 1.93 (m, 1H), 2.60 (m, 1H), 3.08 (m, 1H), 3.50 (m, 1H), 3.59 (s, 3H), 3.66 (s, 2H), 3.76 (s, 3H), 4.65 (d.d, $J=7.8, 9.4$ Hz, 1H), 7.09 (s, 2H), 7.32-7.58 (m, 5H).

(7) 7 \rightarrow 8

To a solution of methyl ester (20.3 g, 73.7 mmol) in
10 methanol (148 ml) was added 1N KOH 148 ml (2 x 73.7 mmol) and the mixture stirred for 3 hr at room temperature. The reaction mixture was poured into water, acidified with 2N HCl, and extracted with ethyl acetate. The extract was washed with brine, dried over Na_2SO_4 , and concentrated in vacuo. The residue was recrystallized from
15 ethyl ether/hexane to obtain carboxylic acid (18.68 g). mp. 88-89°C, yield 96.9%.

Elemental analysis ($C_{11}H_{19}NO_4S$)

Calcd.: C, 50.56; H, 7.33; N, 5.36; S, 12.27

Found : C, 50.34; H, 7.28; N, 5.40; S, 12.17.

20 IR ($CHCl_3$): 1758, 1725 1695.

(8) 8 \rightarrow 9

To a solution of carboxylic acid (18.55 g, 70.98 mmol) in methylene chloride (190 ml) were added triethylamine (23.7 ml, 2.4 x 70.98 mmol) and then ethyl chlorocarbonate (8.1 ml, 1.2 x 70.98
25 mmol) under ice-cooling, and the mixture stirred for 30 min at the same temperature. After the addition of a solution of 4-(dimethyl-t-butyldimethylsilyloxymethyl)aniline (20.22 g, 1.2 x 70.98 mmol) in dimethylformamide (20 ml), the mixture was stirred for



1 hr at the same temperature. The reaction mixture was washed with 2N HCl, 5% NaHCO₃, and H₂O successively, dried over Na₂SO₄, and concentrated in vacuo. The residue was subjected to silica gel column chromatography and fractions eluting with hexane/ethyl acetate (4:1 to 2:1) were collected to obtain a silyl ether (33.57 g) as a foam. Yield 98.4%.

(9) 9 → 10

To a solution of the silyl ether (33.57 g, 69.8 mmol) in tetrahydrofuran (340 ml) was added 1N tetra-n-butylammonium fluoride (77 ml, 1.1 x 69.8 mmol) under ice-cooling and the mixture stirred for 5 hr at room temperature. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with 2N HCl, 5% NaHCO₃, and H₂O successively, dried over Na₂SO₄, and concentrated in vacuo. The residue was subjected to silica gel column chromatography and fractions eluting from hexane/ethyl acetate/methylene chloride (1:1:0.5) to ethyl acetate were collected. Recrystallization from methylene chloride/n-hexane gives an alcohol (24.21 g). MP. 164.6 – 165 °C, yield 94.6%.

20 Elemental analysis (C₁₈H₂₆N₂O₄S)

Calcd.: C, 58.99; H, 7.15; N, 7.64; S, 8.75

Found : C, 59.17; H, 7.26; N, 7.53; S, 8.50.

IR (CHCl₃): 3610, 3410, 3330, 1690, 1602, 1523.

(10) 10 → 11

25 A solution of oxalyl chloride (3.7 ml, 1.5 x 27.29 mmol) in methylene chloride (100 ml) was stirred at -78°C. To the solution was added dropwise a solution of dimethyl sulfoxide (5.8 ml, 3 x 27.29 mmol) in methylene chloride (58 ml) over 10 min. The



mixture was stirred for another 15 min and a solution of the alcohol (10.0 g, 27.29 mmol) in methylene chloride (100 ml) was added over 5 min. After stirring for 30 min at the same temperature, triethylamine (19 ml, 5 x 27.29 mmol) was added. The reaction solution was warmed to room temperature over 30 min, washed with 2N HCl, 5% NaHCO₃, and H₂O successively, dried over Na₂SO₄, and concentrated in vacuo. The residue was subjected to silica gel column chromatography and fractions eluting with hexane/ethyl acetate (1:1) to obtain an aldehyde (9.35 g) as a foam. Yield 94.0%.

10 Elemental analysis (C₁₈H₂₄N₂O₄S 0.2H₂O)

Calcd: C, 58.74; H, 6.68; N, 7.61; S, 8.71

Found: C, 58.62; H, 6.66; N, 7.49; S, 8.82.

IR (CHCl₃): 3400, 1695, 1592.

NMR (CDCl₃): 1.48 (s, 9H), 2.15 (s, 3H), 7.70 (d, J=8.6Hz, 2H), 7.85 (d, J=8.6Hz, 2H), 9.91 (s, 1H).

(11) 11 → 12

To a solution of the aldehyde (6.3 g, 17.29 mmol) in dry toluene (63 ml) were added 2,4-thiazolizinedione (2.02 g, 17.29 mmol), 1M piperidine/toluene (0.86 ml, 0.05 x 17.29 mmol) and 1M acetic acid/toluene (0.86 ml, 0.05 x 17.29 mmol). The mixture was heated to reflux for 2 hr with stirring and dehydrating with molecular sieves. After the reaction mixture was cooled, methyl ethyl ketone was added thereto. The mixture was washed with 2N HCl and then H₂O, dried over Na₂SO₄, and concentrated in vacuo. The residue was subjected to silica gel column chromatography and fractions eluting with methylene chloride/methanol (10:1) were collected and recrystallized from methylene chloride/ethyl ether to obtain an aimed product (7.42 g). mp. 216-217°C (decomp.),



yield 92.5%.

Elemental analysis ($C_{21}H_{25}N_3O_5S_2$)

Calcd.: C, 54.41; H, 5.44; N, 9.06; S, 13.83

Found : C, 54.23; H, 5.53; N, 8.91; S, 13.60.

5 IR (Nujol): 3250, 1742, 1710, 1692, 1670, 1600, 1535.

NMR ($CDCl_3$): 1.49 (s, 9H), 2.16 (s, 3H).

(12) 12 \rightarrow 13

To a suspension of a starting compound (3.0 g, 6.47 mmol) in methanol (30 ml) and methylene chloride (12 ml) was added
10 10N HCl/MeOH (13 ml, 20 x 6.47 mmol) under ice-cooling. After stirring for 3 hr at room temperature, the precipitated crystals were filtered off and rinsed with ethyl ether to give hydrochloride (2.514 g). mp. (decomp.) $> 245^\circ C$, yield 97.2%.

Elemental analysis ($C_{16}H_{18}N_3O_3S_2Cl \cdot 0.3H_2O$)

15 Calcd.: C, 47.41; H, 4.63; N, 10.37; S, 15.82 Cl; 8.75

Found : C, 47.38; H, 4.65; N, 10.35; S, 15.65 Cl; 9.15.

IR (Nujol): 3350, 1728, 1690, 1590.

NMR (d_6 -DMSO): 2.12 (s, 3H), 4.52 (t, $J=8.2$ Hz, 1H), 7.62 (d, $J=8.6$ Hz, 2H) 7.78 (d, $J=8.6$ Hz, 2H), 7.84 (s, 1H).

20 (13) 13 \rightarrow A-1

To a solution of a starting compound (300 mg, 0.75 mmol) in methylene chloride (12 ml) were added triethylamine (0.23 ml, 2.2 x 0.75 mmol) and then acetyl chloride (64 μ l, 1.2 x 0.75 mmol) under ice-cooling and the mixture stirred for 2 hr at the same
25 temperature. After the addition of methyl ethyl ketone, the reaction solution was washed with 2N HCl and H_2O in series, dried over Na_2SO_4 and concentrated in vacuo. The residue was subjected to silica gel column chromatography and fractions eluting with



methylene chloride/methanol (10:1) were collected and recrystallized from acetone/ethyl ether to obtain an aimed product (261 mg). mp. 143-146°C, yield 85.8%.

Elemental analysis ($C_{18}H_{19}N_3O_4S_2 \cdot 0.6H_2O$)

5 Calcd.: C, 51.93; H, 4.89; N, 10.09; S, 15.40

Found : C, 52.05; H, 5.01; N, 10.05; S, 15.23.

Hygroscopicity: 4 µg/min.

IR (Nujol): 3275, 1740, 1702, 1675, 1590.

NMR (d_6 -DMSO): 1.83 (s, 3Hx17/100 E or Z), 2.01 (s, 3Hx83/100 E or Z), 2.10 (s, 13Hx7/100 E or Z), 2.12 (s, 3Hx83/100 E or Z).

Various compounds were synthesized from the corresponding starting materials in a manner similar to those described in Examples above. Physicochemical values of the resultant compounds are shown in Table A, 1 to 5.

15 Table A-1

	Y_1-Y_2	R^1	B	IR(Nujol cm^{-1})	NMR($CDCl_3$ ppm)
A-1	COCH ₃	CH ₃	O	1740 1702	2.01(s, CH ₃) 2.12(s, CH ₃)
-2	OC-	H ₂ C-	S	1705 1588	3.81(s, -CH ₂ -) 7.60(s, -CH=)
-3	"	"	O	1746 1708 1596	3.74(s, -CH ₂ -) 7.62(s, -CH=)
-4	"	H ₂ C-	O	1748 1705 1587	1.35(s, ^t Bu) 3.62(s, CH ₃) 7.62(s, -CH=)
-5	"	H ₂ C-	O	1738 1704 1595	3.88(s, -CH ₂ -) 7.60(s, -CH=)
-6	"	H ₂ C-	O	1735 1695 1673	3.78(s, -CH ₂ -) 7.68(s, -CH=)
-7	"	H ₂ C-	O	1738 1704 1590	3.79(s, -CH ₂ -) 7.62(s, -CH=)



-8	•		O	1738 1704 1590	3.73(s,-CH ₂) 7.63(s,-CH=)
-9	•		O	1739 1704 1591	3.77(s,CH ₃ ×2) 3.81(s,CH ₃) 7.62(s,-CH=)
-10	•		O	1738 1703 1587	2.21(s,CH ₃) 2.32(s,CH ₃ ×2) 7.68(s,-CH=)
-11	•		O	1738 1704 1590	1.51(s,CH ₃) 7.68(s,-CH=) 1.58(s,CH ₃) 1.66(s,CH-)
-12	•		O	1738 1704 1592	5.19(s,-CH<) 7.63(s,-CH=)
-13	COH		S	1705 1655 1587	3.81(s,-CH ₂ -) 7.68(s,-CH=) 8.21(s,CHO)
-14	COCH ₃	•	S	1710 1695 1590	1.96(s,CH ₃) 3.86(s,-CH ₂ -) 7.68(s,-CH=) d-DMSO
-15	OC--CF ₃	CH ₃	S	1700 1615 1584	2.15(s,-CH ₃) 7.45(s,-CH=)



Table A-2

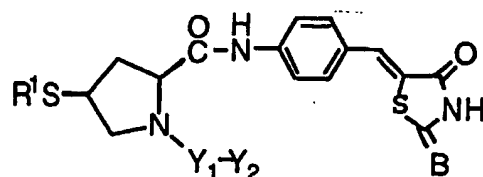
	Y ₁ -Y ₂	R ¹	B	IR(Nujol cm ⁻¹)	NMR(d-DMSO ppm)
A-16	COO ^t Bu		S	1730 1688 1672	1.27(d, CH ₃) 1.30(d, CH ₃) 1.49(s, ^t Bu) CDCl ₃
-17	"		S	1720 1690 1668	1.47(s, ^t Bu) 3.79(s, -CH ₂ =) CDCl ₃
-18	H.HCl	"	S	1720 1684 1590	3.87(s, -CH ₂ -) 7.61(s, -CH=)
-19	CO(CH ₂) ₁₂ CH ₃	CH ₃	S	1715 1702 1592	2.14(s, CH ₃ ×1/5) 2.47(s, CH ₃ ×4/5) CD ₃ OD
-20		"	O	1738 1695 1594	2.09(s, CH ₃)
-21	"	"	S	1701 1585	2.09(s, CH ₃)
-22		"	S		2.13(s, CH ₃) 7.47(s, -CH=)
-23			S	1694 1630 1574 KBr	3.82(s, -CH ₂ ×85/100) 3.88(s, -CH ₂ ×15/100)
-24		"	S	1704 1625 1588 KBr	3.80(s, -CH ₂ ×4/5) 3.88(s, -CH ₂ ×1/5)
-25		CH ₃	O	1745 1710 1695	2.09(s, CH ₃ ×1/5) 2.12(s, CH ₃ ×4/5) 7.72(s, -CH=)
-26	"	"	S	1700 1585	2.13(s, CH ₃) 3.71(s, -CH ₂ -)
-27	"		S	1705 1632 1585	1.23(d, CH ₃) 1.24(d, CH ₃)
-28			S	1702 1647 1585	3.87(s, -CH ₂ -) CDCl ₃
-29		"	S	1699 1586	3.86(s, -CH ₂ -) 7.58(s, -CH=)
-30		"	S	1709 1584	3.80(s, -CH ₂ -) 7.57(s, -CH=)



Table A-3

	Y_1-Y_2	R^1	B	IR(Nujol cm^{-1})	NMR(d -DMSO ppm)
A-31			S	1710 1588	0.90(t, CH_3) 3.86(s, $-\text{CH}_2-$) 7.56(s, $-\text{CH}=\text{N}-$)
-32		.	S	1705 1588	2.70(s, $\text{CH}_3 \times 2$) 3.87(s, $-\text{CH}_2-$) 7.54(s, $-\text{CH}=\text{N}-$)
-33		.	S	1705 1585	1.32(d, CH_3) 1.36(d, $-\text{CH}_2-$) 3.79(s, $-\text{CH}_2-$) CDCl_3
-34		CH_3	S	1710 1698	2.05(s, CH_3) 7.57(s, $-\text{CH}=\text{N}-$)
-35	.	.	O		2.05(s, CH_3) 7.74(s, $-\text{CH}=\text{N}-$)
-36			S	1695 1688	3.79(s, $-\text{CH}_2-$) 7.54(s, $-\text{CH}=\text{N}-$) CDCl_3
-37		.	S	1703 1580 KBr	2.14(s, CH_3) 3.80(s, $-\text{CH}_2-$) 7.59(s, $-\text{CH}=\text{N}-$)
-38		.	S	1700 1589 KBr	2.15(s, CH_3) 3.73(s, $-\text{CH}_2-$) 7.59(s, $-\text{CH}=\text{N}-$)
-39		.	S	1702 1592 KBr	1.33(s, tBu) 7.60(s, $-\text{CH}=\text{N}-$)
-40		CH_3	O	1740 1702 1588	2.13(s, $-\text{CH}_2-$) 7.80(s, $-\text{CH}=\text{N}-$) CDCl_3
-41	.		S	1711 1580	3.74(s, $-\text{CH}_2-$) 8.05(s, $-\text{CH}=\text{N}-$) CDCl_3
-42		.	O	1741 1702 1593	3.69(s, $-\text{CH}_2-$) 7.77(s, $-\text{CH}=\text{N}-$) CDCl_3
-43	.	.	S	1701 1591 KBr	3.76(s, $-\text{CH}_2-$) CDCl_3
-44	.	CH_3	O	1742 1700 1595	2.07(s, CH_3) 7.75(s, $-\text{CH}=\text{N}-$) CD_3OD
-45	.	.	S	1722 1695 1592	2.07(s, CH_3) 7.77(s, $-\text{CH}=\text{N}-$) CD_3OD
-46	.		O	1741 1702 1592	3.66(s, $-\text{CH}_2-$) 3.88(s, $-\text{CH}_3$) 3.82(s, $\text{CH}_3 \times 2$)

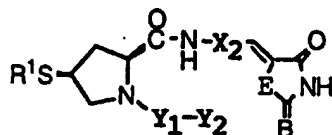
Table A-4



	Y_1-Y_2	R^1	B	IR(KBr cm^{-1})	NMR(CDCl ₃ ppm)
A-47		CH ₃	S	1701 1592	2.05(s, CH ₃) 7.62(s, -CH=)
-48	"	H ₂ C-	S	1700 1592	3.67(s, -CH ₂ -) 7.62(s, -CH=)
-49		CH ₃	S		2.06(s, CH ₃) 3.08(s, -CH ₂ -) 7.74(s, -CH=)
-50		CH ₃	O	1742 1700	2.04(s, CH ₃)
-51		H ₂ C-	S	1706 1581	3.64(s, -CH ₂ -) 7.60(s, -CH=) d-DMSO
-52		"	S	1700 1586	2.80(s, CH ₃ ×2) d-DMSO
-53		"	S	1702 1581	3.88(s, -CH ₂ -) 4.79(AB-d, 1H) 4.86(AB-d, 1H) d-DMSO
-54		"	S	1709 1578	3.71(s, -CH ₂ -) 7.56(s, -CH=)
-55		"	S	1703 1591	3.82(s, -CH ₂ -) 7.59(s, -CH=) d-DMSO
-56		H ₂ C-	S	1703	3.68(s, -CH ₂ -)

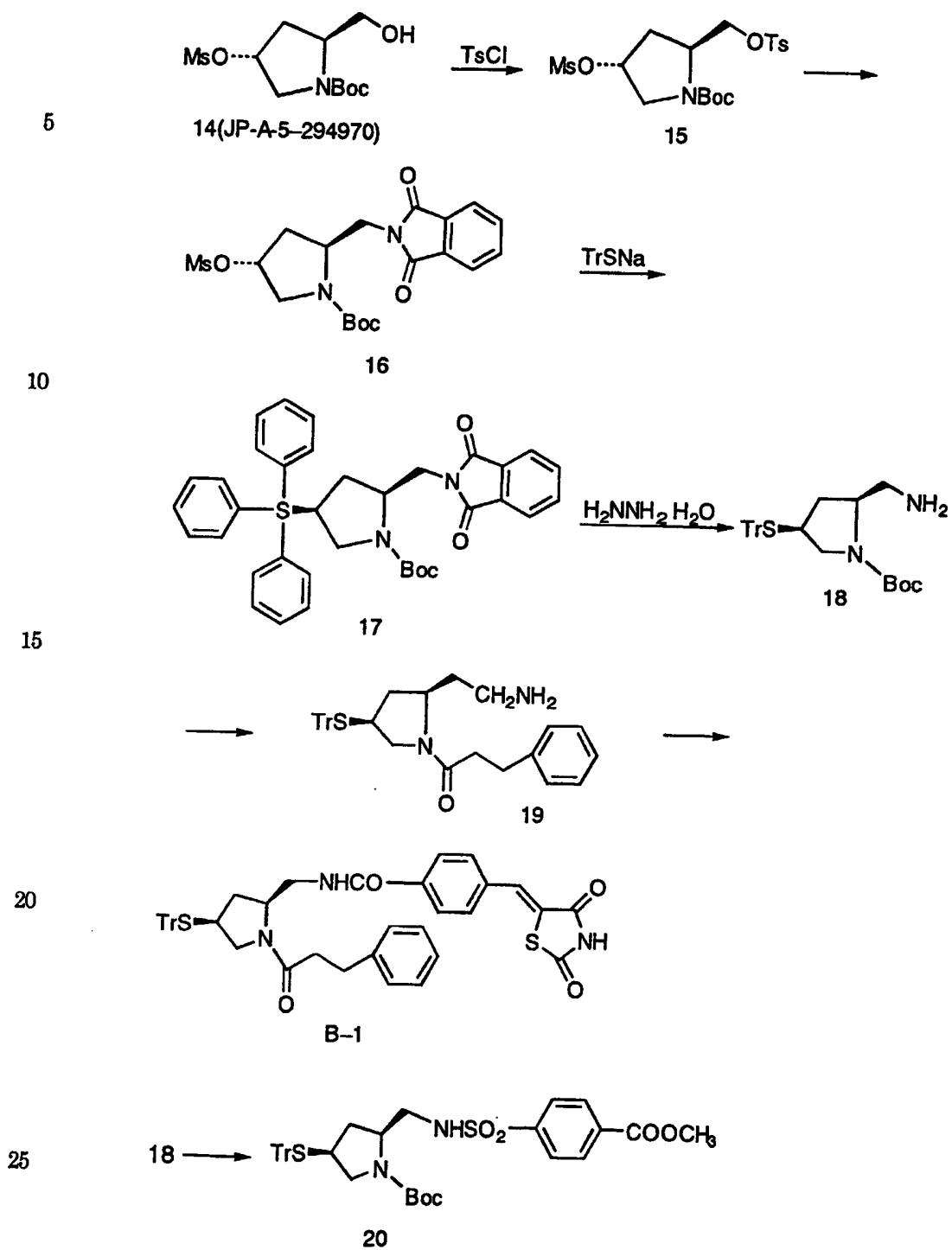


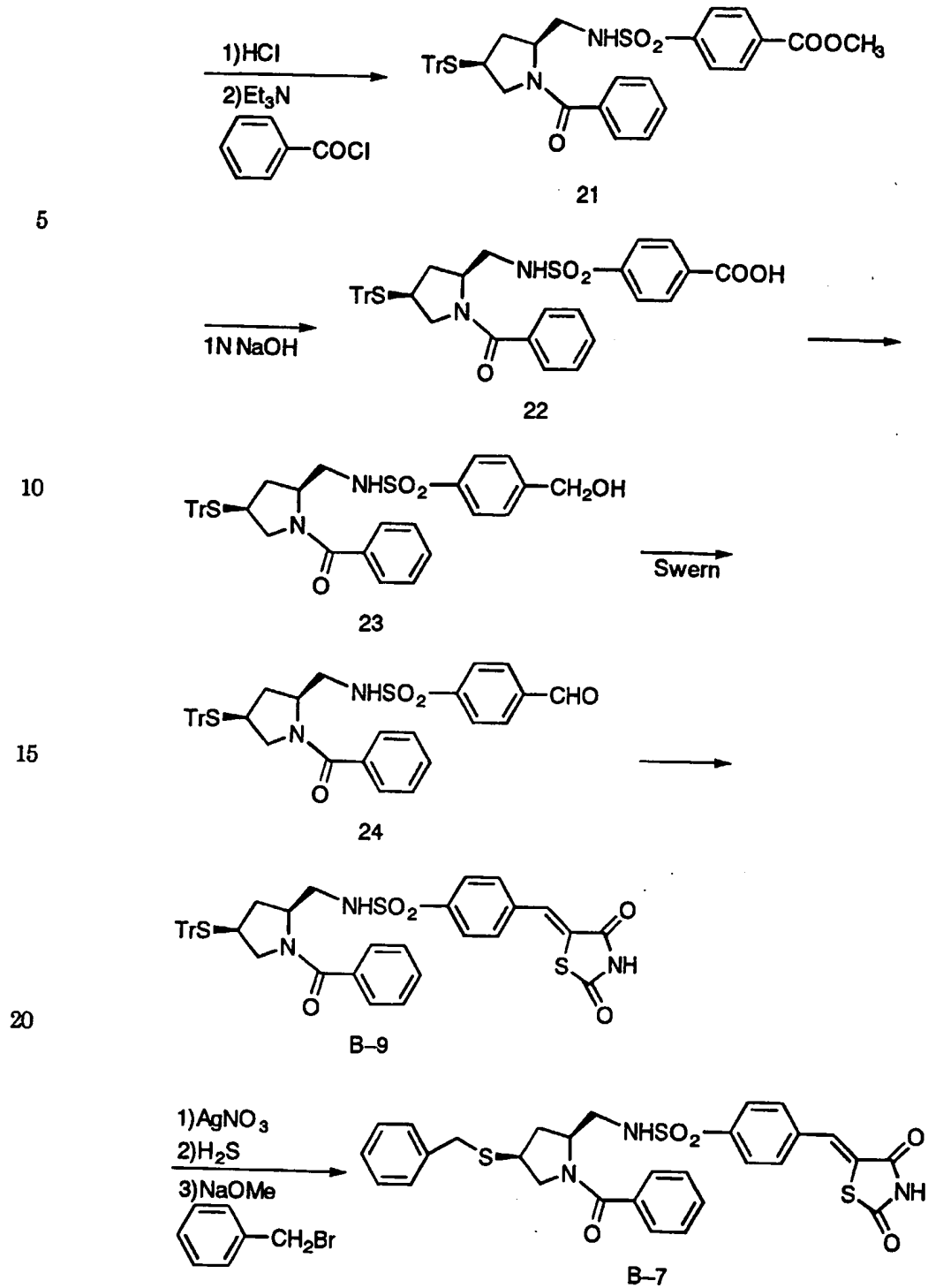
Table A-5



	Y ¹ -Y ²	R ¹	X ₂	B	E	IR(Nujol cm ⁻¹)	NMR(DMSO ppm)
A-57				S	S	1719 1694 1591	3.76(s, -CH ₂ -) 10.40(s, NH)
-58		.	.	S	S	1703 1584	3.77(s, -CH ₂ -) 10.41(s, NH)
-59		.	.	S	S	1686 1588	2.20(s, CH ₃) 2.46(s, CH ₃) 3.80(s, -CH ₂ -) 7.59(s, -CH=)
-60		.		S	S	1711 1600 1537	3.75(s, -CH ₂ -) 8.41(s, -CH= x1/2) 8.45(s, -CH= x1/2) CDCl ₃
-61	.	.	.	S	O	1749 1714 1619	3.77(s, -CH ₂ -) 8.35(s, -CH=) CDCl ₃
-62				S	O	1753 1665 1594	1.41(s, -C(CH ₃) ₃) 6.42(s, NH) CDCl ₃
-63		.	.	S	O	1752 1672 1594	6.70(s, NH) 10.30(s, NH)



Example 2 (Method B₁)



(1) 14 -> 15

To a solution of a starting compound (44.38 g, 150 mmol) in methylene chloride (170 ml) were added triethylamine (25 ml, 1.2x150 mmol), p-toluenesulfonyl chloride (28.6 g, 150 mmol) and dimethylaminopyridine (0.91 g, 0.05 x 150 mmol) under ice-cooling. After stirring overnight at room temperature, the reaction solution was washed with 1N HCl, 5% NaHCO₃, and H₂O successively, dried over Na₂SO₄ and concentrated in vacuo. The residue was subjected to silica gel column chromatography and fractions eluting with hexane/ethyl acetate (1:1) were collected to obtain the tosyl compound (43.4 g) as a gum. Yield 64.4%. A portion was lyophilized from benzene and subjected to elemental analysis.

Elemental analysis (C₁₈H₂₇NO₆S₂O 0.4C₆H₆)

Calcd.: C, 50.96; H, 6.16; N, 2.91; S, 13.34

Found : C, 50.88; H, 6.21; N, 3.11; S, 13.31.

IR (CHCl₃): 1760, 1692, 1600.

NMR (CDCl₃): 1.41 (s, 9H), 2.45 (s, 3H), 3.03 (s, 3H), 5.19 (br-s, 1H).

(2) 15->16

To a solution of a starting compound (43.4 g, 96.5 mmol) in dimethylformamide (300 ml) was added potassiumphthalimide (19.7 g). The mixture was stirred for 6 hr at 60°C, poured into water and extracted with ethyl acetate. The extract was washed with H₂O, dried over Na₂SO₄ and concentrated in vacuo. The residue was subjected to silica gel column chromatography and fractions eluting with hexane/ethyl acetate (1:1) were collected to obtain an aimed product (27.16 g) as foam. Yield 66.3%. A portion was



lyophilized from benzene and subjected to elemental analysis.

Elemental analysis ($C_{11}H_{24}N_2O_7S \cdot 0.1C_6H_6$)

Calcd.: C, 54.46; H, 5.74; N, 6.48; S, 7.42

Found : C, 54.75; H, 5.71; N, 6.08; S, 7.61.

5 IR ($CHCl_3$): 1775, 1718, 1694.

NMR ($CDCl_3$): 1.20-1.50 (m, 9H), 3.02 (s, 3H), 5.23 (m, 1H).

(3) 16→17

To a suspension of 60% sodium hydride (3.3 g, 1.3 x 64 mmol) in dry tetrahydrofuran (100 ml) was added a solution of triphenylmethylmercaptane (24.8 g, 1.4 x 64 mmol) in dry tetrahydrofuran (100 ml) under stirring and ice-cooling over 10 min under a nitrogen atmosphere. The solution was stirred for another 10 min and added to a solution of a starting compound (27.16 g, 64 mmol) in dry tetrahydrofuran (100 ml) under ice-cooling. After stirring overnight at room temperature, the mixture was poured into water and extracted with ethyl acetate. The extract was washed with water, dried over Na_2SO_4 and concentrated in vacuo. The residue was subjected to silica gel column chromatography and fractions eluting with hexane/ethyl acetate (1:1) were collected to obtain an aimed product (30.22 g) as a foam. Yield 74.0%. A portion was lyophilized from benzene and subjected to elemental analysis.

Elemental analysis ($C_{37}H_{36}N_2O_4S \cdot 0.3C_6H_6$)

Calcd.: C, 74.18; H, 6.06; N, 4.46; S, 5.10

25 Found : C, 74.18; H, 6.15; N, 4.33; S, 5.18.

IR ($CHCl_3$): 1775, 1715, 1685.

(4) 17→18

To a solution of a starting compound (30.22 g, 50 mmol)



in methylene chloride (50 ml) and methanol (300 ml) was added hydrazine hydrate (4.85ml, 2 x 50 mmol) and the mixture was heated for 5 hr at 65°C, while distilling methylene chloride away. After cooling, methylene chloride (300 ml) was added to the mixture and
 5 the precipitated crystals were filtered off. The filtrate was washed with H₂O, dried over Na₂SO₄ and concentrated in vacuo. The residue was subjected to silica gel column chromatography and fractions eluting with methylene chloride/methanol (10:1) were collected to obtain the amine (23.7 g) as a foam. Yield 100%.

10 (5) 19->B-1

To a suspension of 4-(2,4-dioxothiazolidin-5-ylidenemethyl)benzoic acid (1.08 g, 1.1 x 3.95 mmol) in dimethylformamide (20 ml) were added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (833 mg, 1.1 x
 15 3.95 mmol) and then 1-hydroxybenzotriazole (534 mg, 3.95 mmol) and the mixture stirred for 10 min at room temperature. After addition of a starting compound (2g, 3.95 mmol) in dimethylformamide (6 ml), the mixture was stirred overnight. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was
 20 washed with 2N HCl, 5% NaHCO₃ and water successively, dried over Na₂SO₄ and concentrated in vacuo. The resultant residue was subjected to silica gel column chromatography. Fractions eluting with hexane/ethyl acetate/dichloromethane (1:2:0.58) were collected and recrystallized from dichloromethane/ethyl ether to
 25 obtain an aimed product (1.675 g). mp. (decomp.) 164-165 °C, yield 57%.

Elemental analysis (C₁₄H₁₃N₃O₄S₂ 1.1CH₂Cl₂)

Calcd.: C, 65.15; H, 5.00; N, 5.05



Found : C, 65.25; H, 5.07; N, 5.13.

IR (CHCl₃): 3388, 1752, 1709, 1658, 1618, 1524, 1423.

NMR (CDCl₃): 1.65 (m, 1H), 1.90 (m, 1H), 2.40-2.80 (m, 5H), 2.90 (t, J=5Hz, 2H), 3.28 (m, 1H), 3.60 (m, 1H), 4.20 (m, 1H), 6.90-7.55 (m, 24H), 7.90 (s, 1H), 9.04 (s, 1H).
 5 (6) 18→20

To a solution of the amine (8 g, 16.85 mmol) in methylene chloride (170 ml) were added triethylamine (3.5 ml, 1.5 x 16.85 mmol) and methyl p-chlorosulfonylbenzoate (4.74 g, 1.2 x 10 16.85 mmol) and the mixture stirred over night at room temperature. The reaction mixture was washed with 2N HCl and then water, dried over Na₂SO₄ and concentrated in vacuo. The residue was subjected to silica gel column chromatography and fractions eluting with ethyl acetate /methanol (4:1) were collected to obtain methyl ester 15 (10.18 g) as a foam. Yield 97.0%.

Elemental analysis (C₃₇H₄₀N₂O₆S₂)

Calcd.: C, 66.05; H, 5.99; N, 4.16; S, 9.53

Found : C, 65.98; H, 5.99; N, 4.16; S, 9.36.

IR (CHCl₃): 1728, 1673, 1598.

20 (7) 20→21

To a solution of the methyl ester (10.18 g, 15.12 mmol) in methanol (150 ml) and methylene chloride (10 ml) was added hydrochloric acid (27 g) under ice-cooling. The mixture was allowed to stand for 10 min at room temperature and concentrated 25 in vacuo. To the residue was added toluene and concentrated in vacuo, which procedure was repeated twice. To a solution of the residue in methylene chloride (150 ml) were added triethylamine (6.3 ml, 3 x 15.12 mmol), then benzoyl chloride (1.93 ml, 1.1 x



15.12 mmol) under ice-cooling. After stirring overnight at room temperature, the reaction mixture was washed with 2N HCl, 5% NaHCO₃, and H₂O successively, dried over Na₂SO₄, and concentrated in vacuo. The residue was subjected to silica gel column chromatography and
 5 fractions eluting with hexane/ethyl acetate (1:1) were collected to obtain an aimed product (9.9 g) as a foam. Yield 96.7%. A portion was lyophilized from benzene and subjected to elemental analysis.

Elemental Analysis (C₃₉H₃₆N₂O₅S₂ 0.2C₆H₆)

10 Calcd.: C, 69.73; H, 5.41; N, 4.05; S, 9.26

Found : C, 69.72; H, 5.55; N, 4.14; S, 8.90.

IR (CHCl₃): 3202, 1728, 1614, 1577.

NMR (CDCl₃): 3.95 (s, -COOCH₃), 4.10 (m, 1H).

(8) 21->22

15 To a solution of a starting compound (methyl ester) (9.4 g, 13.9 mmol) in methanol (100 ml) was added 1N KOH (28 ml, 213.9 mmol) and the mixture was warmed at 50°C for 7 hr. The reaction solution was acidified with 2N HCl in the presence of ethyl acetate. The organic layer was washed with brine, and concentrated
 20 in vacuo to obtain the carboxylic acid (9.2 g) as a foam. Yield 99.9%. A portion was lyophilized from benzene and subjected to the elemental analysis.

Elemental analysis (C₃₈H₃₄N₂O₅S₂ 0.6 C₆H₆, 0.5 H₂O)

Calcd.: C, 69.01; H, 5.36; N, 3.98; S, 9.12

25 Found : C, 69.11; H, 5.44; N, 4.01; S, 8.87.

IR (CHCl₃): 2500-3500br, 1703, 1601, 1571.

(9) 22->23

To a solution of a starting compound (carboxylic acid)



(8.56 g, 13.57 mmol) in dry tetrahydrofuran (90 ml) were added triethylamine (2 ml, 1.1 x 13.57 mmol), and then ethyl chlorocarbonate (1.42 ml, 1.1x13.57 mmol) under ice-cooling. The mixture was stirred for 30 min at the same temperature, and poured
 5 into a suspension of sodium borohydride (1.28 g, 2.5 x 13.57 mmol) in water (30 ml) under ice-cooling. The mixture was stirred for 1 hr at the same temperature and partitioned into a mixture of water and ethyl acetate containing 2N HCl. The organic layer was washed with brine, dried over Na_2SO_4 , and concentrated in vacuo. The
 10 residue was subjected to silica gel column chromatography and fractions eluting with hexane/ethyl acetate (1:2) were collected to obtain the alcohol (7.70 g) as a foam. Yield 87.5%. A portion was lyophilized from benzene and subjected to elemental analysis.

Elemental Analysis ($\text{C}_{38}\text{H}_{36}\text{N}_2\text{S}_2\text{O}_4 \cdot 0.5\text{H}_2\text{O}$)

15 Calcd.: C, 71.59; H, 5.71; N, 4.07; S, 9.32

Found : C, 71.44; H, 5.78; N, 3.96; S, 9.02.

IR (CHCl_3): 3610, 3380, 1616, 1576.

NMR (CDCl_3): 1.54-2.05 (m, 3H), 2.30-2.79 (m, 3H), 2.90-3.03 (m, 1H), 3.20-3.30 (m, 1H), 4.09 (m, 1H), 4.72 (s, arom- CH_2 -) 6.00
 20 (br, 1H), 6.90-7.54 (m, 22H), 7.76 (d, $J=8.5\text{Hz}$, 2H).

(10) 23->24

Under a nitrogen atmosphere, to a solution of oxalyl chloride (1.35 ml, 1.3 x 11.87 mmol) in methylene chloride (40 ml) was added a solution of dimethyl sulfoxide (2.2 ml, 2.6 x 11.86
 25 mmol) in methylene chloride (5 ml) at -78°C over 5 min with stirring. After stirring for 15 min at the same temperature, a solution of a starting compound (7.70 g, 11.87 mmol) in methylene chloride (20 ml) was added thereto over 5 min. The mixture was stirred for



another 15 min and triethylamine (8.24 ml, 5 x 11.87 mmol) was added thereto. The reaction solution was allowed to warm up to room temperature slowly, washed with 2N HCl, 5% NaHCO₃, and H₂O, successively, dried over Na₂SO₄, and concentrated in vacuo. The residue was subjected to silica gel column chromatography and fractions eluting with hexane/ethyl acetate (1:1) were collected to obtain the aldehyde (6.21 g) as a foam. Yield 80.9%. A portion was lyophilized from benzene and subjected to elemental analysis.

Elemental Analysis (C₃₀H₃₄N₂O₄S₂ 0.6C₆H₆ 0.3H₂O)

Calcd.: C, 71.47; H, 5.51; N, 4.01; S, 9.17

Found : C, 71.26; H, 5.44; N, 4.23; S, 8.90.

IR (CHCl₃): 3381, 1709, 1616, 1577.

NMR (CDCl₃): 1.60 (m, 1H), 2.00 (m, 1H), 2.33-2.78 (m, 3H), 2.98 (m, 1H), 3.35 (m, 1H), 4.12 (m, 1H), 6.58 (m, 1H), 6.92-7.57 (m, 20H), 7.90-8.00 (m, 2H), 10.02 (s, 1H).

(11) 24->B-9

Compound B-9 was prepared according to the Knoevenagel reaction in a manner similar to that described in Example 1, (11) for the preparation of compound (12) from compound (11). Yield 65.7%.

Elemental Analysis (C₄₁H₃₅N₃S₃O₅ 0.3H₂O)

Calcd.: C, 65.54; H, 4.78; N, 5.59; S, 12.80

Found : C, 65.61; H, 4.92; N, 5.59; S, 12.59.

IR (CHCl₃): 3388, 1754, 1710, 1609, 1574.

NMR (CDCl₃): 1.56 (m, 1H), 2.00 (m, 1H), 2.35-2.84 (m, 3H), 3.04 (m, 1H), 3.36 (m, 1H), 4.12 (m, 1H), 6.10 (m, 1H), 6.90-7.58 (m, 22H), 7.71 (s, 1H), 7.89 (d, J=8Hz, 2H), 9.47 (s, 1H).

Example 3 (Method B; B-9->B-7)



To a solution of tritylthio derivative (600 mg, 0.8 mmol) in methanol (7 ml) and tetrahydrofuran (2 ml) was added pyridine (0.16 ml, 2.5 x 0.8 mmol) and the mixture stirred under ice-cooling. After the addition of silver nitrate (313 mg, 2.3 x 0.8 mmol) in methanol (1 ml) and water (1 ml), the mixture was stirred for 10 min. The precipitated crystals were filtered off and rinsed with methanol and ethyl ether successively. Hydrogen sulfide gas was bubbled into a suspension of the resultant silver salt in methylene chloride (15 ml) under ice-cooling and stirring for 10 min. The mixture was stirred for another 30 min at room temperature and filtered through Hyflo Super-Cel™ to remove silver salt. The filtrate was concentrated in vacuo to give a thiol as a foam. To a solution of the thiol in methylene chloride (7 ml) were added 1N sodium methoxide solution (1.52 ml, 1.9 x 0.8 mmol) in methanol under ice-cooling, and 5 min later, benzyl bromide (143 µl, 1.5 x 0.8 mmol). After stirring for 30 min, the mixture was poured into water/methyl ethyl ketone containing 2N HCl for partition. The organic layer was washed with water, dried over Na₂SO₄, and concentrated in vacuo. The residue was subjected to silica gel column chromatography and fractions eluting with methylene chloride/methanol (25:1) were collected and recrystallized from acetone/hexane to give an aimed product (289 mg). mp. 212-214°C.

Elemental analysis (C₂₉H₂₇N₃O₃S₃)

Calcd.: C, 58.67; H, 4.58; N, 7.08; S, 16.20

Found : C, 58.57; H, 4.63; N, 7.00; S, 16.00.

IR (Nujol): 3300, 1764, 1705, 1588, 1560, 1455.

NMR (d-DMSO): 3.73 (s, 2H), 4.15 (m, 1H), 7.80 (s, 1H).



The compounds prepared in a manner similar to that described in Examples 2 and 3 are shown in Table B₁, 1 to 2.

Table B₁-1

	Y ₁ -Y ₂	R ¹	B	IR(CHCl ₃ cm ⁻¹)	NMR(CDCl ₃ ppm)
B-1	OC-CH ₂ -C ₆ H ₅	-C(C ₆ H ₅) ₃	O	1752 1709 1658	2.91(t, -CH ₂ -) 7.89(s, -CH=)
-2	OC-C ₆ H ₅	H ₂ C-C ₆ H ₄ (^t Bu) ₂ -OCH ₃	O	1751 1709 1648 1579	1.34(s, ^t Bux2) 3.62(s, CH ₃) 3.67(s, -CH ₂ -)
-3	OC-O-CH ₂ -C ₆ H ₄ -OCH ₃	H ₂ C-C ₆ H ₄ (^t Bu) ₂ -OCH ₃	O	1751 1709 1667	1.42(s, ^t Bux2) 4.88(s, -CH ₂ -)
-4	OC-O-CH ₂ -C ₆ H ₄ -NO ₂	-C(C ₆ H ₅) ₃	O	1751 1710 1611	5.17(s, -CH ₂ -) 7.78(s, -CH=)
-5	OC-C ₆ H ₅	H ₂ C-C ₆ H ₄ -COOCH ₃	S	1722 1655 1032 1576	3.86(s, CH ₃)
-6	.	H ₂ C-C ₆ H ₄ -CONH ₂	S	1703 1639 1563	3.77(s, -CH ₂ -)

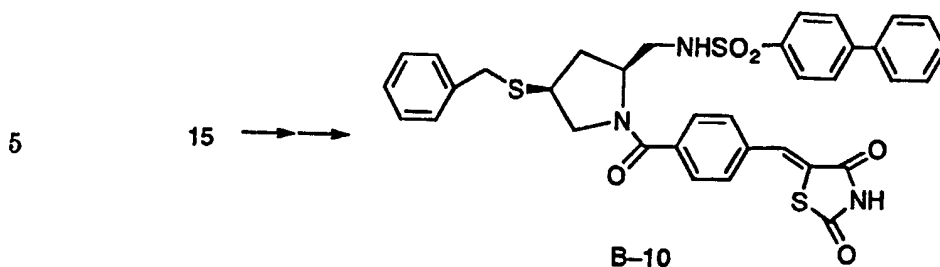
Nujol

d-DMSO

Table B₁-2

	Y ₁ -Y ₂	R ¹	IR(Nujol cm ⁻¹)	NMR(CDCl ₃ ppm)
B-7	OC-C ₆ H ₅	H ₂ C-C ₆ H ₅	1764 1705 1588	3.74(s, -CH ₂ -) d-DMSO
-8	.	-C(C ₆ H ₅) ₂ -H	1748 1706 1605	5.35(s, -CH<)
-9	.	-C(C ₆ H ₅) ₃	1754 1710 1574	7.71(s, -CH=)

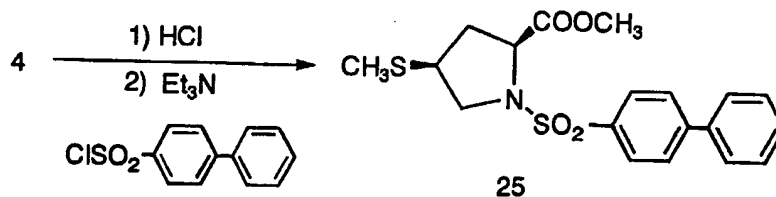


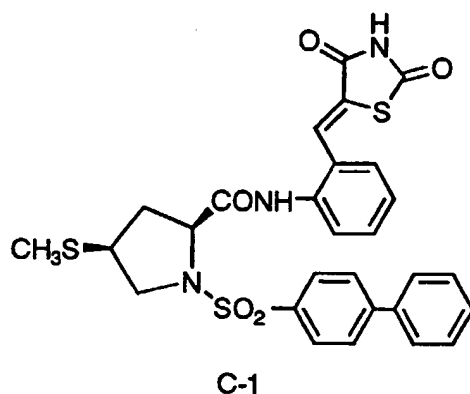
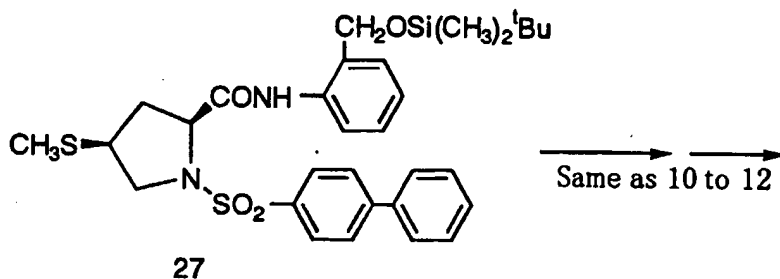
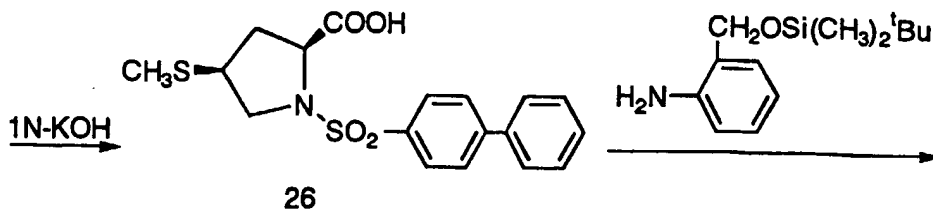
Example 4 (Method B₂)

The compounds prepared in a manner similar to that described in Example 2 are shown in Table B₂.

10 **Table B₂**

		IR(Nujol cm ⁻¹)	NMR(CDCl ₃ ppm)
B-10		1752 1708 1592	3.70(s, -CH ₂ -) 4.27(m, 1H) 7.77(s, -CH=)
15		1745 1706 1617	3.85(m, 1H) 4.48(m, 1H) 5.14(s, -CH<)
-11			

20 **Example 5 (Method c)**



(1) 4 → 25

To a solution of a starting compound (methyl ester) (7.53 g, 27.35 mmol) in ethyl acetate (15 ml) was added 4N HCl (34.2 ml, 5 x 27.35 mmol) under ice-cooling and the mixture stirred for 2 hr at room temperature. After removing the hydrogen chloride gas under reduced pressure, ethyl ether and hexane were added. The precipitated crystals were filtered off and rinsed with ethyl ether to give hydrochloride (5.42 g). To a solution of the hydrochloride (2.0 g, 9.4 mmol) in methylene chloride (40 ml) were added triethylamine (4 ml, 3 x 9.4 mmol), and then p-phenylbenzenesulfonyl chloride (3.73 g, 1.1 x 9.4 mmol) under ice-cooling. The



mixtur was stirred for 2 hr at room temperature. The reaction
 solution was washed with 2N HCl, 5% NaHCO₃ and H₂O, successively,
 dried over Na₂SO₄, and concentrated in vacuo. The residue was
 subjected to silica gel column chromatography and fractions eluting
 5 with hexane/ethyl acetate (1:1) were collected and recrystallized
 from benzene/hexane to give an aimed product (3.64 g). mp.
 95.5-97.5°C, yield 98.9%.

Elemental analysis (C₁₉H₂₁NO₄S₂)

Calcd.: C, 58.29; H, 5.41; N, 3.58; S, 16.38

10 Found : C, 58.24; H, 5.43; N, 3.57; S, 16.40.

IR (Nujol): 1735, 1697, 1594, 1562, 1480, 1460, 1439.

NMR (CDCl₃): 2.03 (m, 1H), 2.08 (s, 3H), 2.54 (m, 1H), 3.02 (m,
 1H), 3.27 (d.d, J=8.6, 10.6Hz, 1H), 3.74 (s, 3H), 3.90 (d.d,
 J=7.2, 10.6Hz, 1H), 4.47 (t, J=7.8Hz, 1H), 7.40-7.55 (m, 3H),
 15 7.57-7.66 (m, 2H), 7.70-7.79 (m, 2H), 7.92-8.01 (m, 1H).

(2) 25→26

To a mixture of the methyl ester (3.64 g, 9.3 mmol)
 in methanol (20 ml) and dimethyl sulfoxide (10 ml) was added 1N
 KOH (19 ml, 2 x 9.3 mmol) and the mixture stirred for 2 hr at room
 20 temperature. The reaction mixture was acidified with 2N HCl in
 the presence of ethyl acetate for partition, washed with brine,
 dried over Na₂SO₄, and concentrated in vacuo to obtain the carboxylic
 acid quantitatively.

(3) 26→27

25 To a solution of a starting compound (755 mg, 2 mmol)
 in dry tetrahydrofuran (5 ml) were added triethylamine (0.42 ml,
 3 mmol) and then isobutyl chlorocarbonate (328 mg, 2.4 mmol) in dry
 tetrahydrofuran (1 ml) under ice-cooling. The mixture was stirred



for 20 min. After the addition of 2-t-butyldimethylsilyloxymethylaniline (950 mg, 4 mmol), the mixture was stirred for 2 hr at room temperature. The reaction solution was poured into water and extracted with ethyl acetate. The
 5 extract was washed with 2N HCl, 5% NaHCO₃, and H₂O, successively, dried over Na₂SO₄, and concentrated in vacuo. The residue was subjected to silica gel column chromatography and fractions eluting with hexane/ethyl acetate (4:1) were collected to obtain an aimed product (1 g). Yield 84.2%.

10 Elemental analysis (C₃₁H₄₀N₂O₄S₂Si)

Calcd.: C, 62.38; H, 6.75; N, 4.69; S, 10.74

Found : C, 62.29; H, 6.68; N, 4.74; S, 10.75.

IR (CHCl₃): 3332, 1678, 1591, 1525, 1453, 1358, 1164, 1133.

NMR(CDCl₃): 0.11(s, 3H), 0.17(s, 3H), 0.94(s, 9H), 2.06(s, 3H),
 15 2.15-2.43(m, 2H), 2.87(m, 1H), 3.52(d.d, J=11.6, 6.6Hz, 1H), 3.85(d.d, J=11.6, 7.0Hz, 1H), 4.24(d.d, J=8.2, 6.4Hz, 1H), 4.74(d, J=13.0Hz, 1H), 4.97(d, J=13.0Hz, 1H), 7.05-8.05(m, 13H), 9.48(brs, 1H).

The objective compound C-1 was obtained in a manner
 20 similar to that described in Example 1, (10) and (12). The compound C-1 and other compounds prepared in a similar manner are shown in Table C.



Table C-1

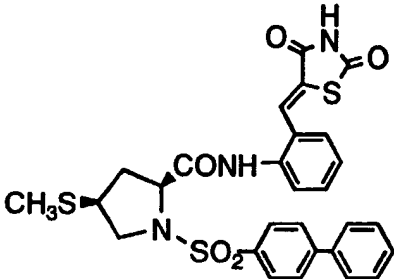
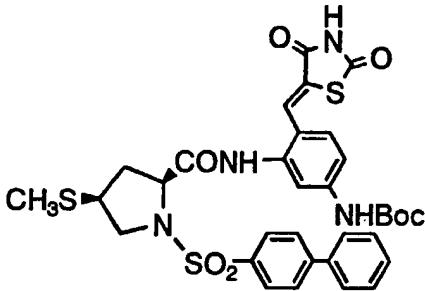
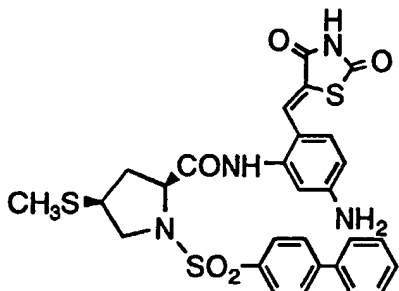
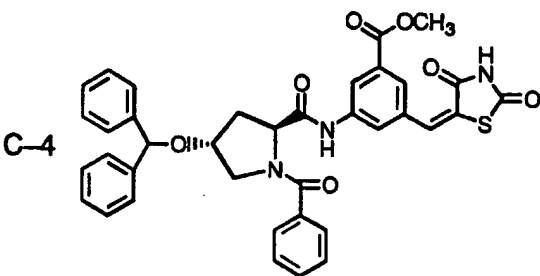
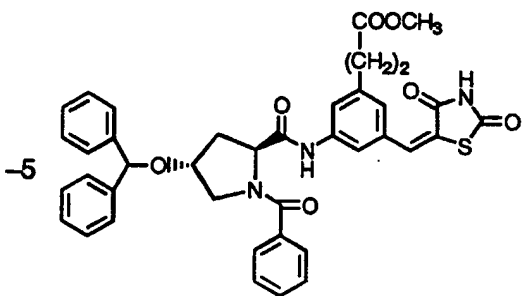
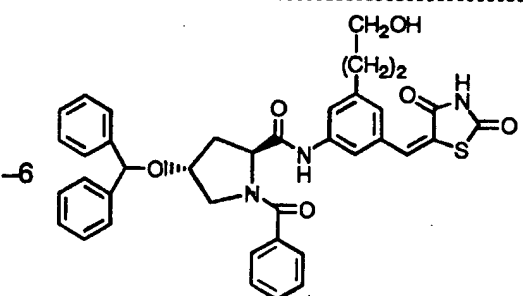
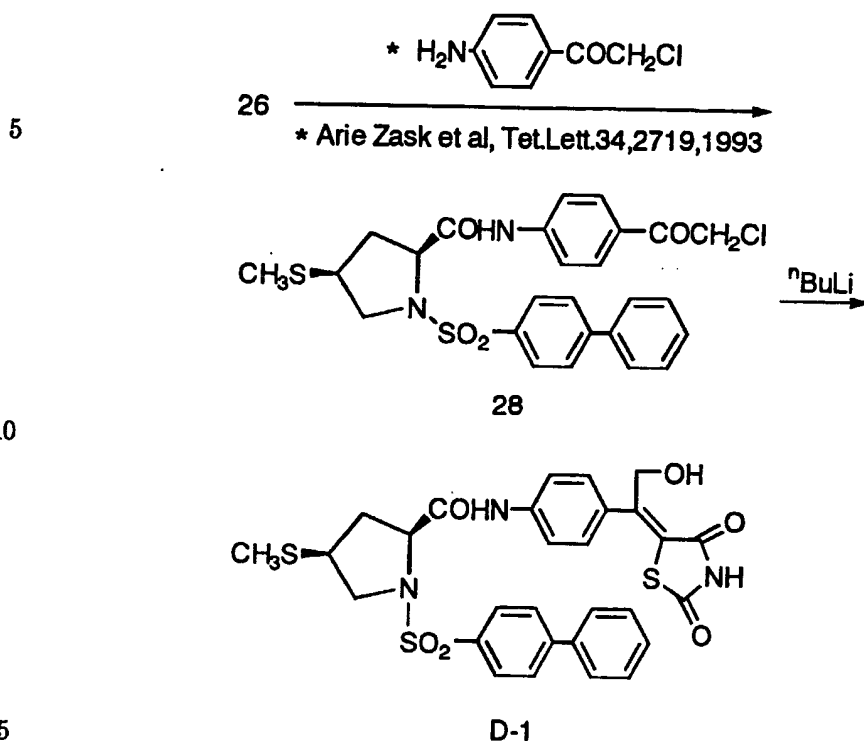
		IR(KBr cm ⁻¹)	NMR(CDCl ₃ ppm)	
5	C-1		1745 1704 1596	2.11(s,CH ₃)
10	-2		1743 1704 1609 1542	1.55(s, ^t Bu) 2.09(s,CH ₃) 7.80(s,-CH=)
15	-3		1742 1701 1609 1544	2.05(s,CH ₃)



Table C-2

		IR(Nujol cm^{-1}) NMR(CDCl_3 ppm)	
5	 <p>C-4</p>	1751 1705 1612 1572	3.92(s, -CH ₃) 5.30(s, -CH<)
10	 <p>-5</p>	1741 1709 1613 1573	3.66(s, -CH ₃) 5.29(s, -CH<) 7.80(s, -CH=)
15	 <p>-6</p>	1742 1703 1610 1571	5.55(s, -CH=) DMSO



Example 6 (Method D)

1) 26->28

To a solution of a starting compound (3.5 g, 9.3 mmol) in methylene chloride (35 ml) were added triethylamine (2.85 ml, 9.3 mmol) and isobutyl chloroformate (1.33 ml, 1.1 x 9.3 mmol) under ice-cooling, and the mixture stirred for 20 min. A solution of 4-amino-2-chloroacetophenone (1.74 g, 1.1 x 9.3 mmol) in dimethylformamide (10 ml) was added to the mixture. After stirring overnight at room temperature, ethyl acetate was added to the reaction solution. The solution was washed with 2N HCl, 5% NaHCO₃, and H₂O, successively, dried over Na₂SO₄, and concentrated in vacuo. The residue was subjected to silica gel column chromatography and fractions eluting with hexane/ethyl acetate (1:1) were collected and recrystallized from acetone/ethyl ether to obtain an aimed



product (2.185 g). mp. 131-134°C, yield 44.4%.

Elemental analysis ($C_{26}H_{25}N_2O_4S_2Cl$)

Calcd.: C, 59.03; H, 4.76; N, 5.29; S, 12.12 Cl; 6.70

Found : C, 58.99; H, 4.83; N, 5.27; S, 12.11 Cl; 6.61.

5 IR (Nujol): 3358, 1707, 1693, 1595, 1560, 1521, 1480, 1459.

NMR ($CDCl_3$): 2.07 (s, 3H), 2.20 (m, 1H), 2.43 (m, 1H), 3.07 (m, 1H), 3.65 (m, 1H), 4.23 (d.d, $J=6, 8$ Hz, 1H), 4.70 (s, 3H), 7.40-8.00 (m, 13H), 9.02 (s, 1H).

(2) 28→D-1

10 To a solution of 2,4-thiazolidinedione (470 mg, 4 mmol) in dry tetrahydrofuran (24 ml) was added 1.62 M n-butyllithium solution (4.94 ml, 2 x 4 mmol) in hexane at -78 °C in an atmosphere of argon and the mixture stirred for 30 min at 0 °C. To the reaction mixture was added a solution of a starting compound (2.12 g, 5 mmol)
15 in dry tetrahydrofuran (8 ml) at -78°C over 3 min. After stirring overnight at room temperature, the mixture was poured into water/methylene chloride containing 2N HCl for partition, washed with water, dried over Na_2SO_4 , and concentrated in vacuo. The residue was subjected to silica gel column chromatography and
20 fractions eluting with methylene chloride/ethyl acetate (3:1) were collected, and pulverized with methylene chloride/ethyl ether to obtain an aimed product (408 mg). Yield 16.7%.

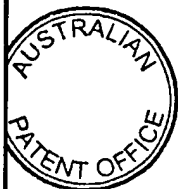
Elemental analysis ($C_{29}H_{27}N_3S_3O_6 \cdot 0.2(C_2H_5)_2O$)

Calcd.: C, 57.31; H, 4.68; N, 6.73; S, 15.40

25 Found : C, 57.11; H, 4.58; N, 6.64; S, 15.14.

IR (Nujol); 3460, 3336, 1736, 1696, 1594, 1560, 1523, 1479.

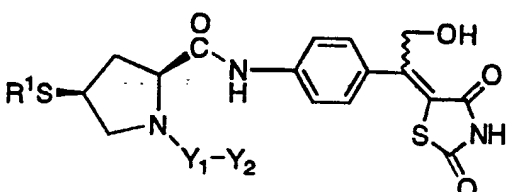
NMR ($CDCl_3$): 2.03 (s, 3/2H), 2.05 (s, 3/2H), 2.20-2.34 (m, 2H), 2.93 (m, 1H), 3.30-3.57 (m, 2H), 3.71 (m, 1H), 4.23 (t, $J=7$ Hz, 1H), 4.44 (s,

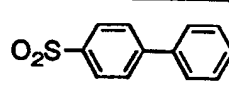
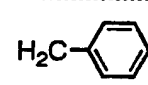
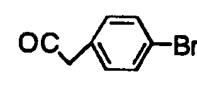


2H), 7.16(d, J=8.6Hz, 2H), 7.40-7.65(m, 7H), 7.78(d, J=8.6Hz, 2H), 7.93(d, J=8.6Hz, 2H), 8.94(s, 1H), 9.09(s, 1H).

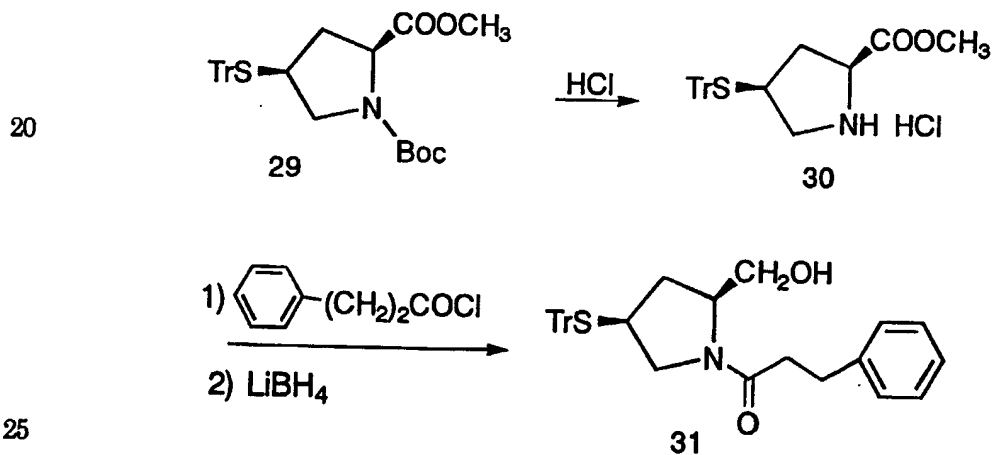
The compounds prepared in a manner similar to the above are shown in Table D.

5 Table D

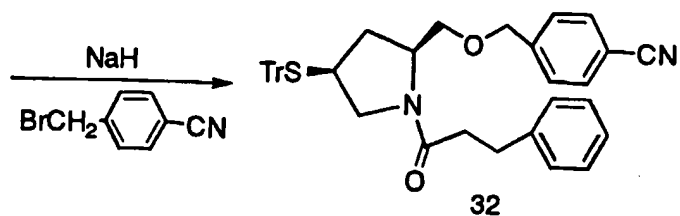


	Y_1-Y_2	R^1	IR(Nujol cm^{-1})	NMR(CDCl_3 ppm)
10	D-1 	CH_3	1736 1696 1594	2.08(s, CH_3) 4.82(d, $-\text{CH}_2-$)
	-2 "	$\text{H}_2\text{C}-$ 	1734 1693 1593	3.68(s, $-\text{CH}_2-$) 4.81(d, $-\text{CH}_2-$)
15	-3 	"	1734 1690 1630 1599	3.57(s, $-\text{CH}_2-\times 1/2$) 3.75(d, $-\text{CH}_2-\times 1/2$) 4.75(d, $-\text{CH}_2-$)

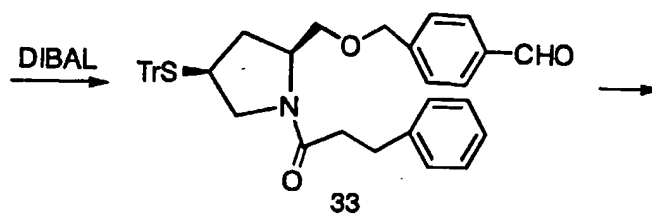
Example 7 (Method E₁)



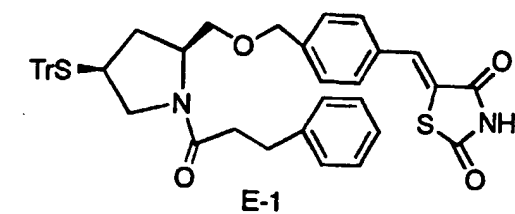
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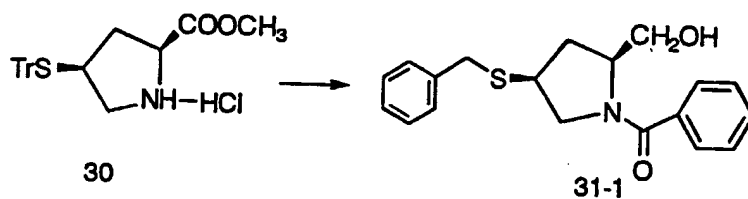
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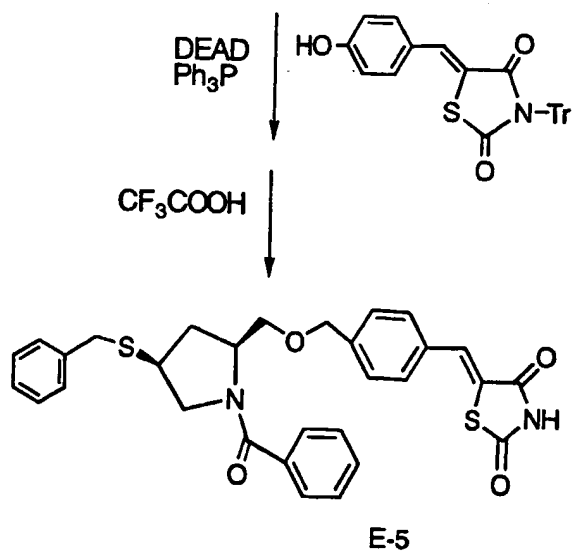
15



20



25



(1) 29→30

Under a nitrogen atmosphere, to a solution of the compound 29 described in Japanese Patent Publication (KOKAI) 5-294970 (USP 5317016) (5.036 g, 10 mmol) in methanol (12 ml) and
5 dichloromethane (30 ml) was added 3.66 M HCl/MeOH (55 ml, 0.2 mole) under ice-cooling with stirring. The mixture was stirred for 5 hr at room temperature. After allowing to stand for 63 hr in a refrigerator, the reaction mixture was concentrated in vacuo, followed by azeotropic distillation with dry toluene to dryness.
10 The aimed product was obtained quantitatively.
NMR (CDCl₃): 1.78-1.93 (1H, m), 2.05-2.30 (1H, m), 3.02 (3H, m), 3.70 (3H, s), 4.18 (1H, bs), 7.18-7.45 (15H, m), 8.78 (1H, bs), 10.88 (1H, bs).

(2) 30→31

15 Under a nitrogen atmosphere, to a solution of the hydrochloride (30) (4.78 g, 10.885 mmol) obtained above in dry dichloromethane (20 ml) were added TEA (triethylamine) (3.6 ml, 26 mmol) and then 3-phenylpropionyl chloride (1.94 ml, 13 mmol) with stirring and under ice-cooling. The mixture was stirred for
20 2 hr at room temperature, poured into ice-water, and extracted with dichloromethane. The extract was washed with water, dried over Na₂SO₄, and concentrated in vacuo. The residue was subjected to silica gel column chromatography and fractions eluting with toluene/ethyl acetate were collected to obtain an aimed product
25 (5.27 g). Yield 90.6%.

NMR (CDCl₃): 1.66-1.82 (1H, m), 2.22-2.37 (3H, m), 2.51-2.56 (1H, m), 2.73-2.99 (4H, m), 3.70 (3H, s), 4.16 (1H, t, J=8.6Hz), 7.18-7.46 (20H, m).



The resultant ester (5.27 g, 9.84 mmol) was dissolved in dry tetrahydrofuran (33 ml). Under a nitrogen atmosphere, to the solution was added lithium borohydride (321 mg, 14.8 mmol) with stirring and under ice-cooling. After stirring for 3 hr at room temperature, the reaction mixture was poured into ice-water containing ammonium chloride, and extracted with ethyl acetate. The extract was washed with brine, dried over Na_2SO_4 , and concentrated in vacuo. The resultant residue was subjected to silica gel column chromatography and fractions eluting with toluene/ethyl acetate were collected, and recrystallized from ether/pentane to obtain an aimed product (4.68 g). mp. 108-112 °C, yield 93.7%.

Elemental analysis ($\text{C}_{33}\text{H}_{33}\text{NO}_2\text{S}$)

Calcd.: C, 78.07; H, 6.55; N, 2.76; S, 6.32

Found : C, 78.06; H, 6.68; N, 2.79; S, 6.19.

IR (CHCl_3): 3328, 1616.

NMR (CDCl_3): 1.25-1.42 (1H, m), 2.12-2.26 (3H, m), 2.35-2.86 (5H, m), 3.40-3.62 (2H, m), 3.85-3.99 (1H, m), 7.14-7.46 (20H, m).

(3) 31-32

Under a nitrogen atmosphere, to a solution of a starting compound (254 mg, 0.5 mmol) obtained above in dry tetrahydrofuran (3 ml) was added sodium hydride (60%, 30 mg, 0.75 mmol) at -70 °C with stirring, and the mixture was stirred for 30 min at room temperature. After cooling to -70 °C, α -bromo-p-tolunitrile (147 mg, 0.75 mmol) was added with stirring, and the mixture stirred for another 18 hr at room temperature. The reaction mixture was poured into water, and extracted with ethyl acetate. The extract was washed with water, dried over Na_2SO_4 , and



concentrated in vacuo. The resultant residue was crystallized from ether/pentane to obtain the product (195 mg, mp 83-85 °C). The mother liquor was subjected to silica gel column chromatography (eluting with toluene/ethyl acetate), and crystallized from
5 ether/pentane to obtain an aimed product (61 mg). Yield, 82%.

IR (CHCl₃): 2224, 1630.

NMR (CDCl₃): 1.84-2.00 (1H, m), 2.11-2.27 (2H, m), 2.31-2.39 (2H, m), 2.55-2.82 (4H, m), 3.54-3.69 (2H, m), 4.00-4.12 (1H, m), 4.50 (2H, s), 7.15-7.63 (20H, m).

10 (4) 32->33

The starting compound (32) (480 mg, 0.771 mmol) prepared in the above was dissolved in dry toluene (3 ml). Under a nitrogen atmosphere, to the solution was added 1M diisobutyl aluminium hydride solution (1.62 ml, 1.62 mmol) in hexane with
15 stirring and under ice-cooling, and the mixture was stirred for 17 hr at room temperature, and for 1 hr while warming at 50 °C. The reaction mixture was poured into ice-water (containing 3.3 ml 1N HCl, pH 4-5), and extracted with ethyl acetate. The extract was washed with water, dried over Na₂SO₄, and concentrated in vacuo.

20 The resultant residue was subjected to silica gel column chromatography (eluting with toluene/ethyl acetate) to obtain an aimed product (106 mg, 22%, powder).

IR (CHCl₃): 1697, 1626, 1609.

NMR (CDCl₃): 1.53-1.63 (1H, m), 1.86-2.03 (1H, m), 2.10-2.20 (1H, m), 2.28-2.63 (1H, m), 2.50-2.95 (5H, m), 3.54-3.70 (2H, m), 4.05 (1H, bs), 4.54 (2H, s), 7.10-7.50 (22H, m), 7.82-7.87 (2H, m), 10.00 (1H, s).

(5) 33->E-1



To a solution of the starting compound (33) (95 mg, 0.152 mmol) obtained in the above in dry toluene (2.6 ml) were added 0.1 M piperidine solution (119 μ l, 0.0119 mmol) in toluene, 0.1M acetic acid solution (119 μ l, 0.0119 mmol) in toluene and 2,4-thiazolidinedione (27 mg, 0.228 mmol). The mixture was heated to reflux for 14 hr, poured into ice-water, extracted with ethyl acetate, washed with water, dried over Na_2SO_4 , and concentrated in vacuo. The resultant residue was subjected to silica gel column chromatography (eluting with toluene/ethyl acetate) to obtain an aimed product (65 mg, foam, 59%).

IR (CHCl_3): 3386, 2858, 2756, 1742, 1702, 1619, 1604.

NMR (CDCl_3): 1.86-2.02 (1H, m), 2.13-2.91 (8H, m), 3.53-3.70 (2H, m), 4.03-4.15 (1H, m), 4.50 (2H, s), 7.13-7.47 (24H, m), 7.76 (1H, s), 9.51 (1H, s).

(6) 31-1 \rightarrow E-5

To a solution of the compounds (31-1) (98 mg, 0.3 mmol) and (31-2) (175 mg, 0.38 mmol) prepared in accordance with the method described in Example 1 above, and triphenylphosphine (88 mg, 0.33 mmol) in THF (5 ml) was added dropwise diethyl azodicarboxylate (DEAD) (50 μ l, 0.32 mmol) under ice-cooling. After stirring for 10 min at the same temperature, the reaction mixture was allowed to warm to room temperature and stirred overnight. The solvent was removed by distillation in vacuo. The residue was subjected to silica gel column chromatography (eluting with toluene/ethyl acetate (10:1)) to obtain the ether (56 mg, 24%). To a solution of the ether in dichloromethane (2 ml) was added trifluoroacetic acid (0.1 ml, 1.3 mmol) under ice-cooling, and the mixture stirred for 1 hr. The mixture was then stirred for 2 hr



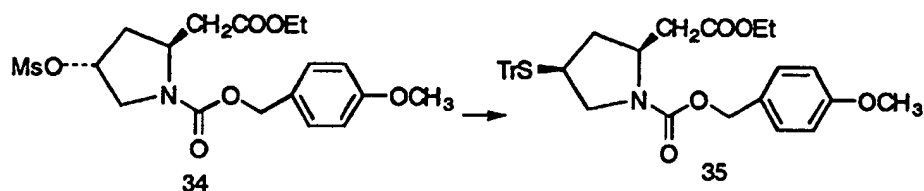
at room temperature. The solvent was removed in vacuo to leave a residue, which was subjected to preparative thin-layer chromatography (developing with dichloromethane/ethyl acetate (3:1)) to obtain an aimed product (30 mg, 78%).

5 IR (KBr): 1739,1700,1596,1509.

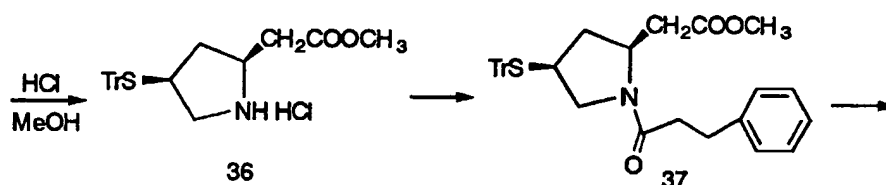
NMR (CDCl₃): 1.95-2.18 (1H, m), 2.40-2.59 (1H, m), 2.90-3.10 (1H, m), 3.20-3.55 (2H, m), 3.72 (2H, s), 4.25-4.65 (3H, m), 7.00-7.50 (14H, m), 7.56 (1H, s) 8.55-8.75 (1H, brs).

Example 8 (Method E₂)

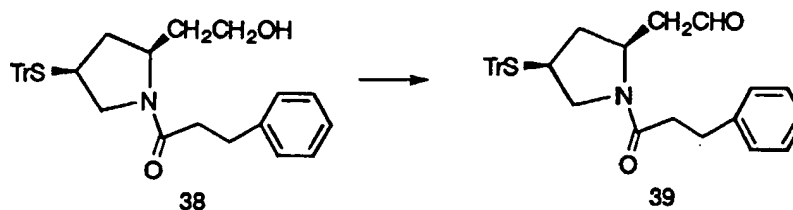
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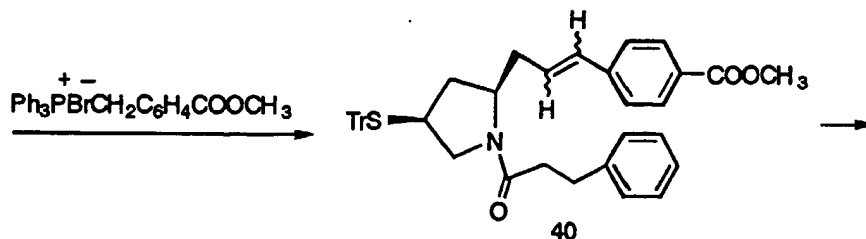
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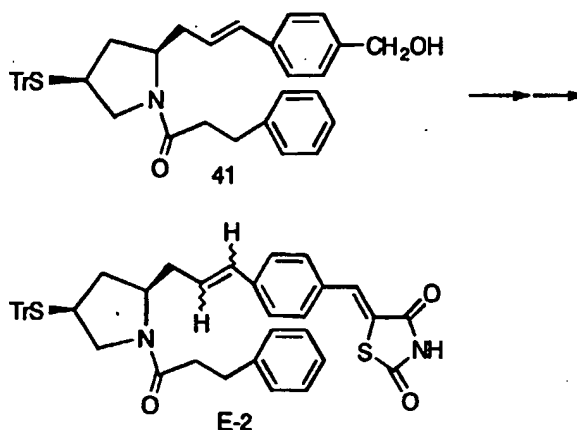


20



25





(1) 34→35

Under a nitrogen atmosphere, to a suspension of sodium hydride (1.129 g, 60%, 28.2 mmol) in dry tetrahydrofuran (26 ml) was added a solution of triphenylmethylmercaptane (8.4 g, 30.4 mmol) in tetrahydrofuran (26 ml) with stirring and under ice-cooling. After the addition of a solution of a starting compound (34) (9.02 g, 21.72 mmol) in tetrahydrofuran (26 ml), the mixture was stirred for 21 hr at room temperature. The reaction solution was poured into ice-water, extracted with ethyl acetate, washed with brine, dried over Na_2SO_4 , and concentrated in vacuo. The resultant residue was subjected to silica gel column chromatography (eluting with hexane/ethyl acetate) to obtain the compound (35) (8.44 g, 65%).

NMR (CDCl_3): 1.23 (3H, t, $J=7.0\text{Hz}$), 1.48-1.65 (1H, m), 2.37 (2H, q, $J=7.0\text{Hz}$), 2.68-3.25 (4H, m), 3.78-3.96 (1H, m), 3.84 (3H, s), 4.05-4.15 (2H, m), 4.84-5.08 (2H, m), 6.80-6.95 (2H, m), 7.20-7.45 (17H, m).

(2) 35→36

The compound (36) was prepared in quantitative yield by treating the compound (35) (5.861 g, 9.84 mmol) in a manner



similar to that used for the synthesis of the compound (30). The resultant compound (36) was dried by azeotropic distillation with dry toluene before subjecting to the synthesis of the compound (37).

(3) 36->37

5 The compound (36) (9.84 mmol) obtained in the above as a residue was treated in exactly the same manner as that for the synthesis of the compound (31) to give the compound (37) in 97% yield.

IR (CHCl₃): 1731, 1631.

10 NMR (CDCl₃): 1.52-1.68 (1H, m), 2.10-3.08 (10H, m), 3.65 (3H, s), 4.07-4.1 (1H, m), 7.12-7.47 (20H, m).

(4) 37->38

 The foamy compound (37) (1.774 g, 3.23 mmol) obtained above was reduced by treating in exactly the same manner as that
15 for the synthesis of the compound (31) to give the compound (38) in 55% yield.

IR (CHCl₃): 3396, 1616.

 NMR (CDCl₃): 1.43-1.58 (2H, m), 1.64-1.86 (1H, m), 2.13-2.21 (2H, m), 2.39-2.59 (2H, m), 2.67-2.83 (4H, m), 2.93 (1H, bs), 3.24-
20 3.51 (2H, m), 4.23 (1H, bs), 7.12-7.45 (20H, m).

(5) 38->39

 Under a nitrogen atmosphere, to a solution of dimethyl sulfoxide (371 µl, 5.23 mmol) in dry dichloromethane (1.2 ml) was added a solution of oxalyl chloride (227 µl, 2.6 mmol) in
25 dichloromethane (3.6 ml) with stirring and under cooling -45°C. The mixture was stirred for 45 min at -45 °C. After the addition of a solution of a starting compound (38) (961 mg, 1.84 mmol) in dichloromethane (1.2 ml) over 10 min, the reaction mixture was



stirred for 45 min at the same temperature. To the mixture was added a solution of triethylamine (1.28 ml, 9.2 mmol) in dichloromethane (1.2 ml), and the mixture allowed to stand overnight at room temperature. The reaction solution was washed
5 with dilute hydrochloric acid, dried over Na_2SO_4 , and concentrated in vacuo. The resultant residue was subjected to silica gel column chromatography (eluting with hexane/ethyl acetate) to obtain an aimed compound (690 mg). Yield 72%.

IR (CHCl_3): 1718, 1629.

10 NMR (CDCl_3): 1.41-1.61 (2H, m), 2.12-2.20 (2H, m), 2.32-2.82 (6H, m), 2.95-3.07 (1H, m), 4.06-4.20 (1H, m), 7.13-7.49 (20H, m), 9.69 (1H, s).

(6) 39→40

Under a nitrogen atmosphere, to a solution of a
15 starting compound (312 mg, 0.6 mole) obtained above in ethanol (7 ml) were added separately prepared methyl 4-(bromotriphenylphosphoniummethyl)benzoate (442 mg, 0.9 mmol) and triethylamine (251 μl , 1.8 mmol) with stirring. The mixture was heated to reflux for 14 hr. The reaction solution was poured into ice-water,
20 extracted with ethyl acetate, washed with water, dried over Na_2SO_4 , and concentrated in vacuo. The resultant residue was subjected to silica gel column chromatography (eluting with toluene/ethyl acetate) to obtain an aimed product as a mixture of E- and Z-compounds (269 mg). Yield 69%.

25 IR (CHCl_3): 1713, 1628.

NMR (CDCl_3): 1.40-1.69 (1H, m), 2.11-3.00 (10H, m), 3.91 (3H, s), 3.90-4.0 (1H, m), 5.51-5.64 & 6.07-6.22 & 6.40-6.55 (2H, m, E & Z mix), 7.15-7.49 (22H, m), 7.96-8.02 (2H, m).



(7) 40→41

The starting compound (40) (239 mg, 0.367 mmol) prepared in the above was reduced with lithium borohydride (80 mg, 10mmol) in exactly the same manner as that for the synthesis of
5 the compounds (27, 34) to obtain the aimed product (41) (158 mg) as a mixture of E- and Z-compounds. Yield. 69%.

IR (CHCl₃): 3596,3408,1626.

NMR (CDCl₃): 1.44-1.65 (1H, m), 2.09-2.95 (10H, m), 3.89-4.03 (1H, m), 4.67 (2H,s), 5.39-5.53 & 5.94-6.10 & 6.36-6.52 (2H, m, E & Z
10 mix), 7.11-7.44 (24H, m).

The resultant compound (41) was then treated in a manner similar to that described in Example 1 to obtain an aimed compound E-2.

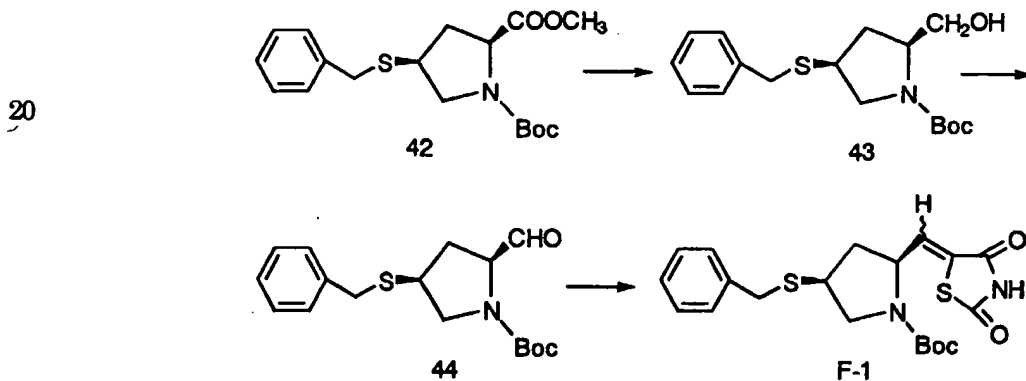
The compounds obtained in a manner similar to that
15 described in Examples 7 and 8 are shown in Table E.



Table E

		IR(cm ⁻¹)	NMR(CDCl ₃ ppm)
E-1		1742 1702 1619 1604	4.50(s, -CH ₂ -) 7.76(s, -CH=)
5		CHCl ₃	
-2		1743 1703 1622 1600	5.60(m, -CH=) 6.48(d, -CH=) 7.72(s, -CH=)
		CHCl ₃	
-3		1740 1701 1619 1601	7.78(s, -CH=)
10		Nujol	
-4		1740 1700 1620 1600	5.13(s, -CH<) 7.79(s, -CH=)
		Nujol	
-5		1739 1700 1596	3.72(s, -CH ₂ -) 7.56(s, -CH=)
15		Nujol	

Example 9 (Method F)



25

(1) 42→43

To a solution of methyl ester (632 mg, 1.80 mmol) in dry tetrahydrofuran (20 ml) was added lithium borohydride (59 mg,



1.5 x 1.8 mmol) with stirring and under ice-cooling. The mixture was stirred for 30 min at the same temperature and then for 4 hr at room temperature. To the reaction solution were added methanol (0.5 ml) and then ice-water (50 ml) under ice-cooling. After
5 adjusting the pH to 2 with 10% HCl, and the reaction solution was extracted with ethyl acetate. The extract was washed with water, brine, dried over Na₂SO₄, and concentrated in vacuo. The residue was subjected to silica gel column chromatography and fractions eluting with hexane/ethyl acetate (2:1) were collected to obtain
10 the alcohol (578 mg). Yield 99.3%.

NMR (CDCl₃): 1.44 (s, 9H), 2.30 (m, 1H), 3.01 (m, 1H), 3.63 (m, 3H), 3.76 (s, 2H), 3.90 (m, 1H), 4.80 (br. s, 1H), 7.31 (m, 5H).
(2) 43→44

To a solution of the alcohol (1.08 g) in dimethyl
15 sulfoxide (2 ml) was added triethylamine (1.5 ml) under ice-cooling, followed by addition of a solution of sulfur trioxide-pyridine complex (1.63 g) in dimethyl sulfoxide (15 ml). The mixture was stirred for 20 min at room temperature, diluted with ethyl acetate (200 ml) for partition, washed with water and brine, dried over
20 Na₂SO₄, and concentrated in vacuo. The residue was subjected to silica gel column chromatography and fractions eluting with hexane/ethyl acetate (2:1) were collected to obtain the aldehyde (607 mg). Yield 56.3%.

The starting compound was then recovered (33.4%).

25 Elemental analysis (C₁₇H₂₃NO₃S 0.2H₂O)

Calcd.: C, 62.82; H, 7.26; N, 4.31; S, 9.86

Found : C, 62.99; H, 7.33; N, 4.34; S, 9.81.

IR (Film): 1732, 1696, 1394, 1255, 1163, 1117.



NMR(CDCl₃): 1.44(s, 9x5/8H), 1.47(s, 3/8H), 2.12(m, 1H), 2.37(m, 1H), 3.18(m, 1H), 3.29(m, 3/8H), 3.42(d.d, J=4.2, 11.7Hz, 5/8H), 3.56-3.77(m, 3H), 4.03(m, 5/6H), 4.14(m, 3/8H), 7.22-7.37(m, 5H), 9.61(d, J=2.1Hz, 5/8H), 9.66(d, J=1.5Hz, 3/8H).

5 (3) 44->F-1

A mixture of aldehyde (570 mg), rhodanine (240 mg), 1M acetic acid (in toluene, 0.1 ml) and 1M piperidine (in toluene, 0.1 ml) in toluene (25 ml) was heated to reflux for 3 hr, and distilled under reduced pressure to remove the solvent. The resultant residue was subjected to silica gel column chromatography and fractions eluting with hexane/ethyl acetate (2:1) were collected to obtain an aimed product (597 mg). Yield 77.1%.
Elemental analysis (C₂₀H₂₄N₂O₃S, 0.4H₂O)

Calcd.: C, 54.13; H, 5.63; N, 6.31; S, 21.67

15 Found : C, 54.17; H, 5.56; N, 6.36; S, 21.77

IR (KBr): 3439, 1728, 1699, 1631, 1392, 1207.

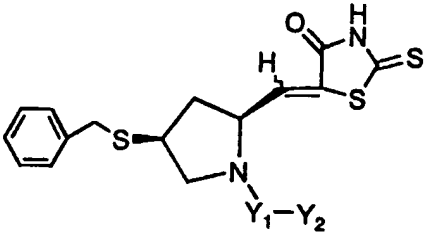
NMR(CDCl₃): 1.30-1.55 (m, 9H), 1.71(m, 1/2H), 1.95(m, 1/2H), 2.10 (m, 1/2), 2.48(m, 1/2H), 2.98-3.34(m, 2H), 4.40-4.00 (m, 1H), 3.75 (s, 1/2H), 3.76 (s, 1/2H), 4.30-4.80 (m, 1H), 6.76 (d, J=5.4Hz, 1/2H),
20 6.89 (d, J=6.1Hz, 1/2H), 7.31(m, 5H), 9.60(br.s, 1H).

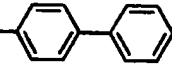
The compounds obtained in a manner similar to that described in Example 9 above are shown in Table F.



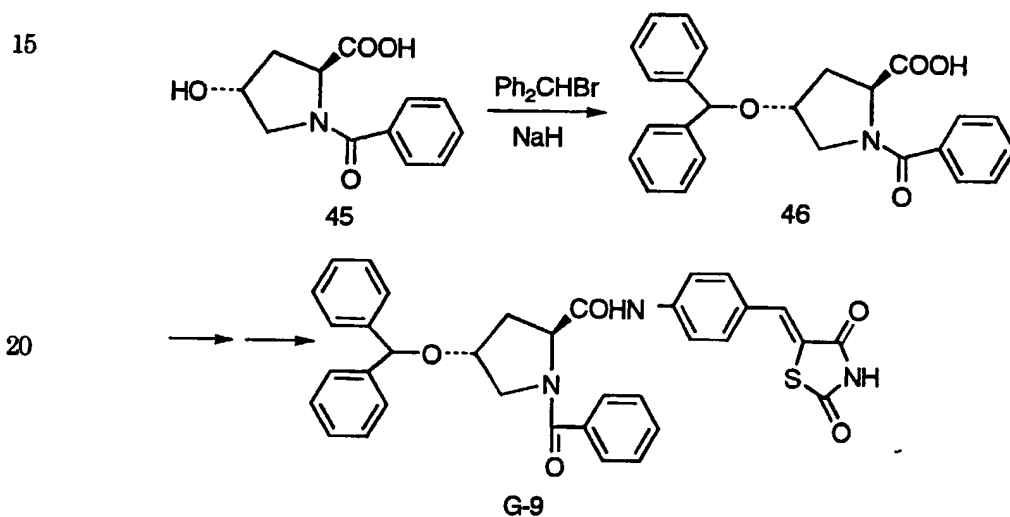
Table F

5



	Y ₁ -Y ₂	IR(KBr cm ⁻¹)	NMR(CDCl ₃ ppm)
F-1	COO ^t Bu	1728 1699 1631	3.75(s, -CH ₂ -X1/2) 3.76(s, -CH ₂ -X1/2) 6.76(s, -CH=X1/2) 6.89(s, -CH=X1/2)
10	-2 O ₂ S- 	1727 1630	3.64(s, -CH ₂ -X1/2) 3.66(s, -CH ₂ -X1/2) 4.29(s, -CH=X1/2) 4.43(s, -CH=X1/2)

Example 10 (Method G)



(1) 45→46

25 Under a nitrogen atmosphere, to a solution of a starting compound (5.34 g, 22.7 mmol) in dimethylformamide (23 ml) were added bromodiphenylmethane (6.73 g, 1.2 x 22.7 mmol), and then 60% sodium hydride (1.81 g, 2 x 22.7 mmol) under ice-cooling. The



mixture was stirred overnight at room temperature. After the addition of water, the reaction mixture was washed with ethyl ether. The aqueous layer was acidified with 2N HCl in the presence of ethyl acetate for partition, washed with brine, dried over Na_2SO_4 , and
5 concentrated in vacuo. The residue was subjected to silica gel column chromatography and fractions eluting with methylene chloride/methanol (25:1) were collected to obtain an aimed product (3.97 g). Yield 43.6%.

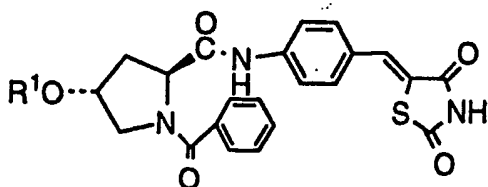
NMR (CDCl_3): 2.46 (d.d, $J=5.0, 8.4\text{Hz}$, 2H), 3.58 (d.d, $J=11.8, 4.0\text{Hz}$,
10 1H), 3.71 (d, $J=12.6\text{Hz}$, 1H), 4.18 (m, 1H), 4.45 (m, 1H), 4.96 (t, $J=8.4\text{Hz}$, 1H), 5.30 (s, 1H), 7.13-7.54 (m, 15H).

The product above was treated in a manner similar to that described in Example 1 to yield the objective compound G-9.

15 The compounds obtained in a manner similar to that described in Example 10 above are shown in Table G.



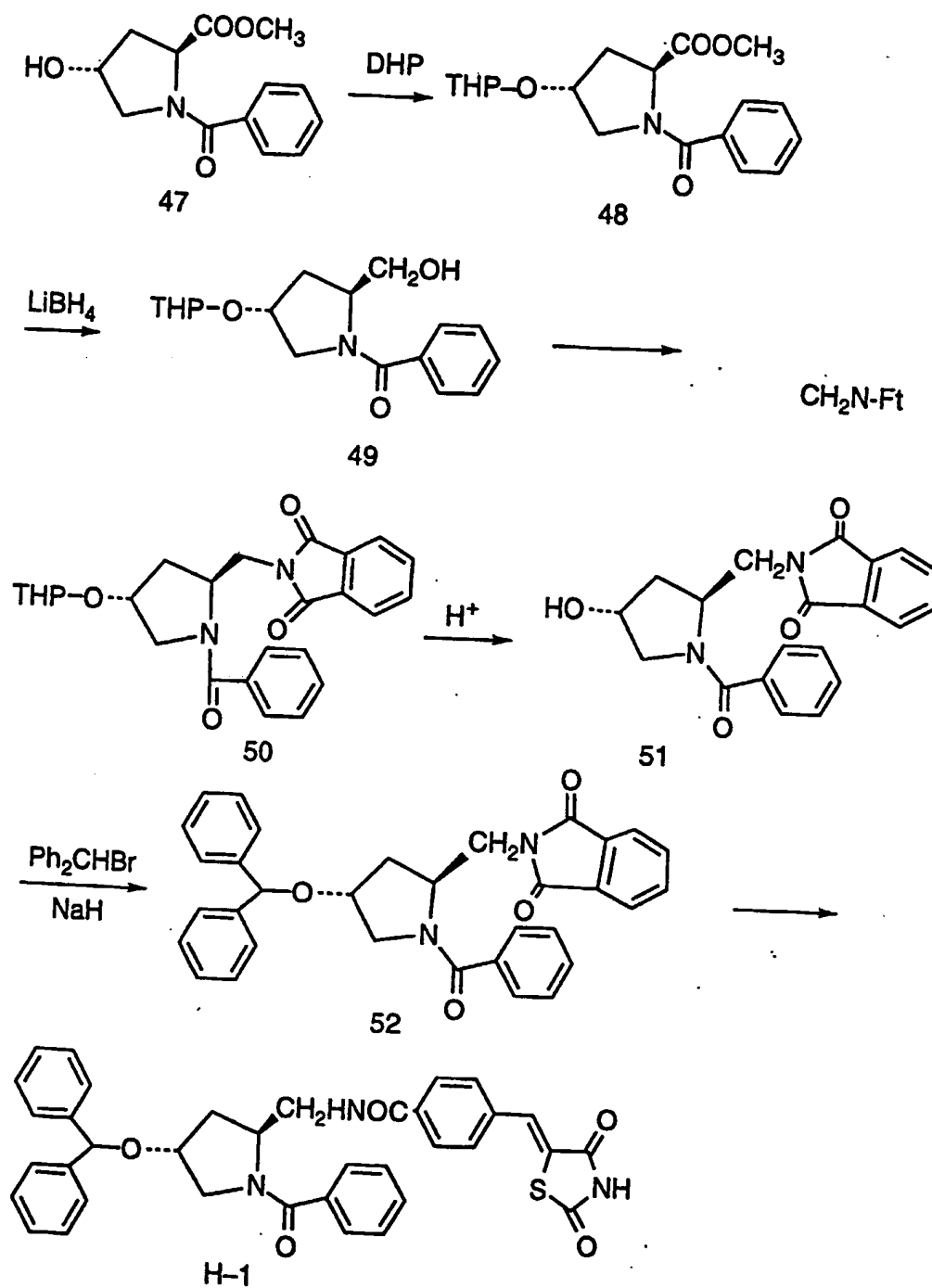
Table G



	R ¹	IR(CHCl ₃ cm ⁻¹)	NMR(CDCl ₃ ppm)
G-1		1739 1705 1615	1.58(s, CH ₃) 1.59(s, CH ₃) 1.66(s, CH ₃)
-2		1739 1704 1615	4.32(d, 1H) 4.42(d, 1H)
-3		1738 1693 1608	4.35(d, 1H) 4.42(d, 1H)
-4		1748 1706 1615	4.47(d, 1H) 4.60(d, 1H)
-5		1739 1704 1620	4.38(d, 1H) 4.47(d, 1H)
-6		1747 1705 1614	2.20(s, CH ₃) 2.24(s, CH ₃ ×2) 4.33(d, 1H) 4.46(d, 1H)
-7		1747 1705 1614	3.81(s, CH ₃) 3.82(s, CH ₃ ×2) 4.33(d, 1H) 4.42(d, 1H)
-8		1745 1704 1589	4.39(d, 1H) 4.49(d, 1H)
-9		1748 1706 1601	5.34(s, 1H)
-10		1746 1705 1600	5.28(s, 1H) 6.90(d, 1H) 6.99(d, 1H)
-11		1745 1704 1589	4.80(d, 1H) 4.89(d, 1H)
-12		1742 1703 1618	4.48(d, 1H) 4.56(d, 1H)



Example 11 (Method H)



(1) 47->48

To a solution of methyl ester (20 g, 80.2 mmol) in methylene chloride (8 ml) were added 3,4-dihydro-2H-pyran (8 ml, 1.1 x 80.2 mmol) and p-toluenesulfonic acid (0.3 g), and the mixture stirred for 7 hr at room temperature. After the addition of triethylamine (0.2 g), the mixture was washed with water, dried over Na₂SO₄, and concentrated in vacuo. The residue was subjected to silica gel column chromatography and fractions eluting with hexane/ethyl acetate (1:2) were collected to obtain an aimed product as a gum quantitatively.

NMR (CDCl₃): 1.35-1.90 (m, 6H), 2.14 (m, 1H), 2.46 (m, 1H), 3.30-3.90 (m, 4H), 3.79 (s, 3H), 4.36-4.87 (m, 3H), 7.35-7.90 (m, 5H).

(2) 48->49

To a solution of the ester in dry tetrahydrofuran (120 ml) was added lithium borohydride (2.62 g, 1.5 x 80.2 mmol) under ice-cooling. After stirring for 1 hr at room temperature, ethanol and 2N HCl were added under ice-cooling (pH = about 5). The mixture was extracted with ethyl acetate, washed with 5% NaHCO₃ and H₂O, successively, dried over Na₂SO₄, and concentrated in vacuo. The residue was subjected to silica gel column chromatography and fractions eluting with ethyl acetate were collected to obtain the aldehyde (22.86 g) as a gum. Yield 93.3%. A portion was lyophilized from benzene and subjected to the elemental analysis.

Elemental analysis (C₁₇H₂₃NO₄ 0.1C₆H₆)

Calcd.: C, 67.50,; H, 7.60; N, 4.47

Found : C, 67.73; H, 7.69; N, 4.29.

IR (CHCl₃): 3351br, 1610, 1602, 1574.

NMR (CDCl₃): 1.30-1.88 (m, 7H), 2.30 (m, 1H), 2.70 (m, 1H), 3.26-3.90



(m, 6H), 4.26 (m, 1H) 4.43-4.70 (m, 2H), 7.35-7.58 (m, 5H).

(3) 49->50

Under a nitrogen atmosphere, to a solution of triphenylphosphine (24.13 g, 1.2 x 74.7 mmol) in dry tetrahydrofuran (150 ml) was added a solution of diisopropyl azodicarboxylate (16.9ml, 1.15 x 74.7 mmol) in dry tetrahydrofuran (120 ml) at -78°C over 15 min. To the mixture was then added a solution of phthalimide (12.64 g, 1.15 x 74.7 mmol) in dry tetrahydrofuran (250 ml) at -53 °C over 15 min. A solution of a starting compound (22.8 g, 74.7 mmol) in dry tetrahydrofuran (150 ml) was then added over 10 min and the mixture stirred for 1 hr at 0°C and then overnight at room temperature. The reaction solution was concentrated in vacuo and flushed with toluene. The residue was subjected to silica gel column chromatography and fractions eluting with hexane/ethyl acetate (1:1) were collected to obtain an aimed product as an oil quantitatively.

Elemental analysis ($C_{25}H_{26}N_2O_5$)

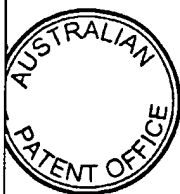
Calcd.: C, 69.11; H, 6.03; N, 6.45

Found : C, 69.36; H, 6.19; N, 6.44.

IR ($CHCl_3$): 1774, 1715, 1629, 1578.

(4) 50->51

To a solution of the previously prepared starting compound in methanol (150 ml) were added water (3 ml) and p-toluenesulfonic acid (1.42 g, 0.1 x 74.7 mmol), and the mixture stirred for 15 hr at room temperature. After the addition of triethylamine (1 ml), the reaction mixture was concentrated in vacuo. Water was added to the residue, followed by extraction with methylen chloride. The extract was washed with water, dried over



Na₂SO₄, and concentrated in vacuo. The residue was subjected to silica gel column chromatography and fractions eluting with hexane/ethyl acetate (1:1) were collected and recrystallized from methylene chloride/ethyl ether to obtain an aimed product (22.94 g). mp. 180-181 °C, yield 87.8% from compound 45.

Elemental analysis (C₂₀H₁₈N₂O₄)

Calcd.: C, 68.56; H, 5.18; N, 8.00

Found : C, 68.30; H, 5.34; N, 7.95.

IR (Nujol): 3472, 1774, 1712, 1610, 1578.

10 NMR (CDCl₃): 1.60-2.30 (m, 3H), 3.39 (d, J=10Hz, 1H), 3.60 (d. d, J=10, 4Hz, 1H), 3.95 (d, J=6Hz, 2H), 4.30 (s, 1H), 5.08 (m, 1H), 7.27-7.45 (m, 5H), 7.60-7.88 (m, 4H).

(5) 51->52

To a solution of a starting compound (4 g, 11.4 mmol) in dimethylformamide (20 ml) was added 60% sodium hydride (457 mg, 11.4 mmol), and the mixture stirred for 5 min under ice-cooling. After adding bromodiphenylmethane (2.96 g, 1.05 x 11.4 mmol), the mixture was stirred for 2 days at room temperature and then for 6 hr at 65°C. The reaction solution was poured into water/ethyl acetate for partition. The organic layer was washed with water and dried over Na₂SO₄ and concentrated in vacuo. The residue was subjected to silica gel column chromatography and fractions eluting with hexane/ethyl acetate (1:1) were collected to obtain an aimed product (1.857 g) as a foam. Yield 31.5%.

25 Elemental analysis (C₃₃H₂₈N₂O₄)

Calcd.: C, 76.72; H, 5.46; N, 5.42

Found : C, 76.76; H, 5.64; N, 5.22.

IR (CHCl₃): 1774, 1725, 1630, 1603, 1427.



NMR (CDCl₃): 1.88 (m, 1H), 2.34 (m, 1H), 3.50 (d, J=4Hz, 2H), 3.93 (m, 2H), 4.08 (m, 1H), 5.04 (m, 1H), 5.18 (s, 1H), 7.05-7.40 (m, 15H), 7.60-7.87 (m, 4H).

(6) 52->H-1

5 A starting compound (1.8 g, 3.48 mmol) was treated in a manner similar to that described in Example 2 for the preparation of compound (18) from compound (17) to yield the amine. To a suspension of 4-(2,4-dioxothiazolidin-5-ylidenemethyl)benzoic acid (1.04 g, 1.2x3.48 mmol) in
10 dimethylformamide (10 ml) were added water soluble carbodiimide hydrochloride (0.8 g, 1.2 x 3.48 mmol) and hydroxybenzotriazole (0.56 g, 1.2 x 3.48 mmol), and the mixture stirred for 30 min. After adding the amine in dimethylformamide (5 ml), the mixture was stirred overnight. The reaction solution was poured into water
15 and extracted with methyl ethyl ketone. The extract was washed with water, dried over Na₂SO₄ and concentrated in vacuo. The residue was subjected to silica gel column chromatography, and fractions eluting with ethyl acetate were collected to yield an aimed product (879 mg) as a foam. Yield 40.9%.

20 Elemental analysis (C₃₆H₃₁N₃O₅S 0.3H₂O)

Calcd.: C, 69.39; H, 5.11; N, 6.74; S, 5.15

Found : C, 69.43; H, 5.14; N, 6.58; S, 4.94.

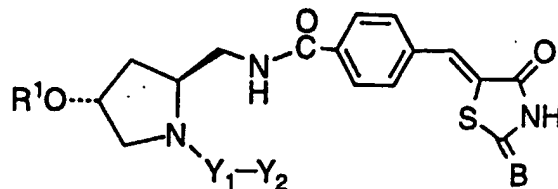
IR (CHCl₃): 3390, 3323, 1750, 1709, 1650, 1610, 1533, 1498.

NMR (CDCl₃): 1.84 (m, 1H), 2.53 (m, 1H), 3.35-3.95 (m, 4H), 4.10
25 (m, 1H), 4.82 (m, 1H), 5.24 (s, 1H), 7.10-7.55 (m, 18H), 7.74 (s, 1H), 7.94 (d, J=8Hz, 2H), 8.76 (m, 1H).

The compounds prepared in a manner similar to those described above are shown in Table H.



Table H-1



	Y_1-Y_2	R^1	B	IR(Nujol cm^{-1})	NMR(d-DMSO ppm)
H-1			O	1750 1709 1650 CHCl ₃	5.24(s, -CH<) 7.74(s, -CH=x3/4) 7.80(s, -CH=x1/4) CDCl ₃
-2			O	1748 1707 1654	4.35(ABd, 1H) 4.41(ABd, 1H) 4.52(ABd, 1H) 4.55(ABd, 1H)
-3		"	O	1749 1707 1655 1619 KBr	2.31(s, CH ₃) 4.54(s, -CH ₂ -) 7.84(s, -CH=)
-4		CH ₃	O	1748 1707 1654 1612 KBr	2.67(s, CH ₃) 4.04(s, -CH ₂ -) 7.71(s, -CH=)
-5	"		O	1749 1709 1658 1620 KBr	3.94(s, -CH ₂ -) 4.02(ABd, 1H) 4.13(ABd, 1H) 7.84(s, -CH=)
-6	COO ^t Bu	"	O	1743 1724 1665 1625	
-7	"	"	S	1733 1716 1666 1625	



Table H-2

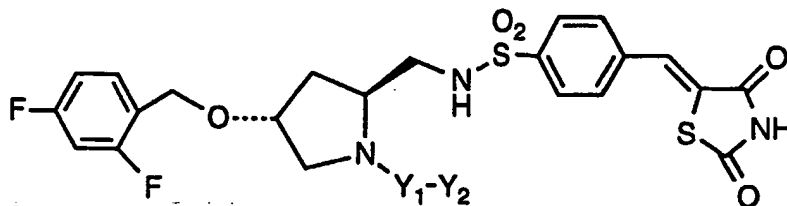
				IR(Nujol cm ⁻¹)	NMR(CDCl ₃ ppm)
H-8			O	1746 1706 1619 1542	4.99(s, -CH ₂ -) 7.73(s, -CH=)
-9			O	1746 1706 1612 1542	4.96(s, -CH ₂ -) 7.75(s, -CH=)
-10			O	1745 1705 1637 1605 KBr	4.50(s, -CH ₂ -) 5.25(s, -CH<) 7.75(s, -CH=)
-11			O	2230 1747 1698 1647 1610 KBr	5.48(s, -CH<) 7.82(s, -CH=) acetone
-12			O	1746 1707 1607 KBr	5.26(s, -CH<) 5.74(ABd, -CH ₂ -) 5.78(ABd, -CH ₂ -) 7.75(s, -CH=)
-13			O	1747 1707 1610 KBr	5.24(s, -CH<) 5.86(s, -CH ₂ -) 7.71(s, -CH=)
-14			O	1750 1708 1646 KBr	0.14(s, -CH ₃) 0.34(s, -CH ₃) 1.01(s, -C(CH ₃) ₃) 5.43(s, -CH<) 7.81(s, -CH=)

Table H-3

	Y_1-Y_2	R^1	B	IR(KBr cm^{-1})	NMR(CDCl ₃ ppm)
H-15			O	1759 1708 1610 1540	2.27(s, -CH ₃) 2.28(s, -CH ₃) 5.41(s, -CH<) 7.78(s, -CH=)
-16			O	1752 1708 1610 1541	2.26(s, -CH ₃) 5.41(s, -CH<) 7.75(s, -CH=)
-17			O	1748 1707 1655 1540	5.42(s, -CH<) 7.79(s, -CH=)
-18			O	1749 1708 1662 1619 CHCl ₃	4.54(s, -CH ₂ -) 7.73(s, -CH=)

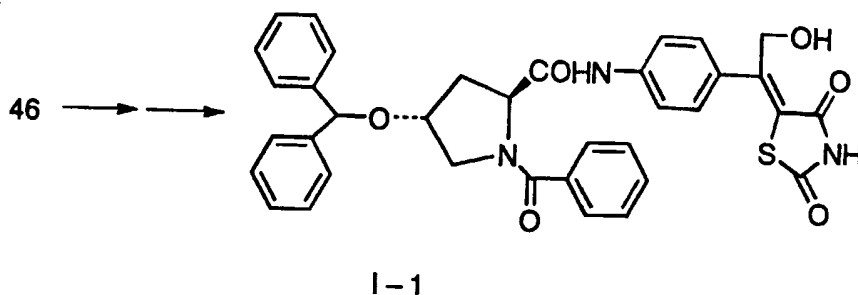


Table H-4



	Y_1-Y_2	IR(KBr cm^{-1})	NMR(ppm)
H-19			4.30(ABd, 1H) 4.32(ABd, 1H) 4.38(ABd, 1H) 4.53(ABd, 1H) 7.83(-CH=) $d\text{-DMSO}$
-20		1750 1710 1620 1605	3.92(s, -CH ₂ -) 4.04(ABd, 1H) 4.12(ABd, 1H) 7.85(s, -CH=) CDCl_3



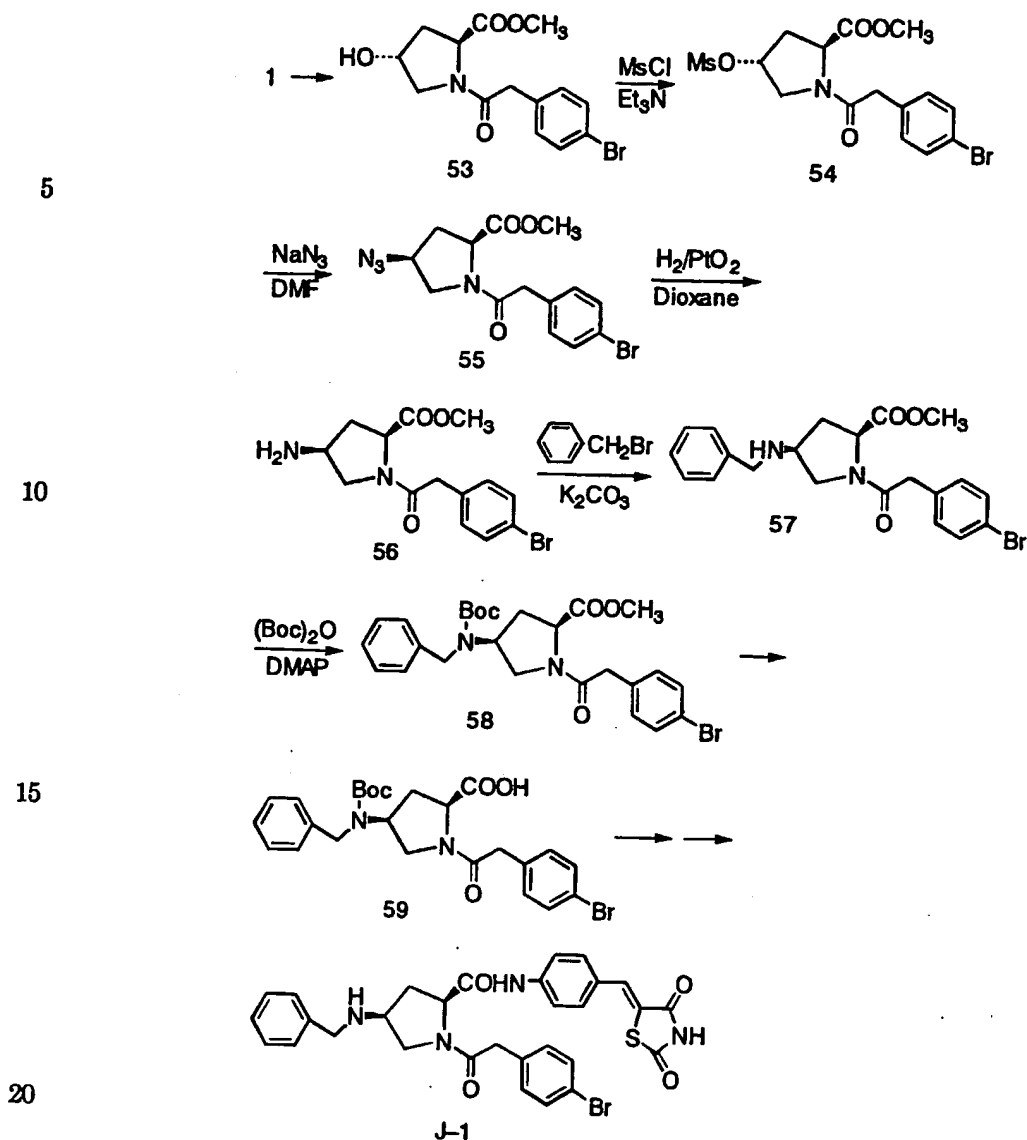
Example 12 (Method I)

Compound I-1 having a hydroxymethyl group was prepared using the compound (46) described in Example 10 in a manner similar to that used for the preparation of compound (28). Physicochemical values of the compound I-1 and those obtained in a similar manner are shown in Table I

Table I

	R ¹	IR(CHCl ₃ cm ⁻¹)	NMR(CDCl ₃ ppm)
I-1	HC(Ph) ₂	1738	4.37(m, 1H)
		1700	4.74(m, 1H)
		1600	5.14(m, -CH ₂ -)
		1532	
-2	C(Ph) ₃	1738	4.50(m, 1H)
		1700	4.74(m, 1H)
		1600	
		1578	



Example 13 (Method J)

(1) 1→53

To a solution of 4-hydroxy-L-proline methyl ester hydrochloride (15.16 g, 83.47 mmol) in dichloromethane (448 ml) were added triethylamine (52.4 ml, 4.5 x 83.47 mmol), 4-bromo-p-phenylacetic acid (21.54 g, 1.2 x 83.47 mmol), and then 2-chloro-1,3-dimethylimidazolinium chloride (21.17 g, 1.5 x 83.47 mmol) under ice-cooling. The mixture was stirred for 10 min at



the same temperature, then allowed to warm up to room temperature, stirred for 1 hr and 40 min, and poured into water/dichloromethane containing dil. HCl for partition. The dichloromethane layer was washed with water, saturated aqueous sodium bicarbonate, and water, dried over MgSO_4 , and concentrated in vacuo. The residue was subjected to silica gel column chromatography and fractions eluting with ethyl acetate were collected and recrystallized from dichloromethane/ethyl ether to obtain prism-like crystals (15.74 g, mp. 135.0–136.0°C). Yield 55.1%.

10 Elemental analysis ($\text{C}_{14}\text{H}_{16}\text{BrNO}_4$)

Calcd.: C, 49.14; H, 4.71; N, 4.09 Br; 23.35

Found : C, 49.23; H, 4.73; N, 4.19 Br; 23.25.

IR (CHCl_3): 3615, 3440, 1747, 1650, 1596, 1490, 1419, 1403.

NMR (CDCl_3): 1.94–2.12 (m, 1H), 2.14–2.33 (m, 1H), 2.55 (d, $J=4\text{Hz}$, 1H), 3.42–3.87 (m, 2H), 3.62 (s, 2H), 3.72 (s, 3H), 4.39–4.60 (m, 1H), 4.58 (t, $J=8\text{Hz}$, 1H), 7.14 (d, $J=8\text{Hz}$, 2H), 7.44 (d, $J=8\text{Hz}$, 2H).
(2) 53→54

To a solution of 4-hydroxyproline derivative (53) (16.326 g, 47.71 mmol) in dichloromethane (56 ml) were added triethylamine (8.65 ml, $1.3 \times 47.71\text{ mmol}$), and then methanesulfonyl chloride (4.06 ml, $1.1 \times 47.71\text{ mmol}$) under ice-cooling. After stirring for 1 hr at the same temperature, the reaction solution was poured into water/dichloromethane containing dil. HCl for partition. The dichloromethane layer was washed with water, saturated aqueous sodium bicarbonate and water, dried over Na_2SO_4 , and concentrated in vacuo. The residue was subjected to silica gel column chromatography and fractions eluting with toluene/ethyl acetate (1:1) were collected to obtain a mesylated compound (19.98



g). Yield 99.6%. A portion was lyophilized from benzene and subjected to elemental analysis.

Elemental analysis ($C_{15}H_{18}BrNO_6S \cdot 0.1C_6H_6$)

Calcd.: C, 43.77; H, 4.38; N, 3.27; Br, 18.67; S, 7.49

5 Found : C, 44.03; H, 4.49; N, 3.47; Br, 19.08; S, 7.50.

IR ($CHCl_3$): 1748, 1658, 1598, 1490, 1427.

NMR ($CDCl_3$): 2.13-2.32 (m, 1H), 2.48-2.66 (m, 1H), 3.00 (s, 3H), 3.50-3.94 (m, 2H), 3. (s, 2H), 3.75 (s, 3H), 4.62 (t, $J=8Hz$), 5.22-5.36 (m, 1H), 7.15 (d, $J=8Hz$, 2H), 7.46 (d, $J=8Hz$, 2H).

10 (3) 54->55

To a solution of the mesylate (19.81 g, 47.14 mmol) in dimethylformamide (154 ml) was added sodium azide (9.19 g, 3 x 47.14 mmol). The mixture was heated at 60 °C with stirring for 9 hr, and poured into water/ethyl acetate for partition. The
15 organic layer was washed with water (x2) and brine, dried over $MgSO_4$ and concentrated in vacuo to obtain an azide compound (17.08 g, oil). Yield 98.7%.

IR ($CHCl_3$): 2102, 1747, 1652, 1593, 1487, 1424.

NMR ($CDCl_3$): 2.10-2.25 (m, 1H), 2.37-2.57 (m, 1H), 3.44-3.86 (m, 2H), 3.65 (s, 2H), 3.75 (s, 3H), 4.15-4.29 (m, 1H), 4.48 (d.d, $J_1=8Hz$, $J_2=2Hz$, 0.3H), 4.63 (d.d, $J_1=9Hz$, $J_2=5Hz$, 0.7H), 7.17 (d, $J=9Hz$, 2H), 7.46 (d, $J=9Hz$, 2H).
20

(4) 55->56

To a solution of the azide compound (16.61 g, 45.23
25 mmol) in dioxane (220 ml) was added platinum oxide (2 g), and catalytic reduction was carried out. The reaction solution was filtered and concentrated in vacuo to yield an amine (18.97 g) as a syrup.



IR (CHCl₃): 3372,1742,1646,1487,1434.

NMR (CDCl₃): 1.70-1.94 (m, 3H), 2.31-2.53 (m, 1H), 3.34 (d.d, J₁=10Hz, J₂=4Hz, 1H), 3.46-3.80 (m, 2H), 3.64 (s, 2H), 3.75 (s, 3H), 4.38-4.53 (m, 1H), 7.16 (d, J=8Hz, 2H), 7.45 (d, J=8Hz, 2H).

5 (5) 56->57

To a solution of the amine (18.97 g, 45.23 mmol) in acetonitrile (222 ml) were added potassium carbonate (9.38 g, 1.5 x 45.23 mmol) and then benzyl bromide (5.92 ml, 1.1 x 45.23 mmol) under ice-cooling. The mixture was stirred for 10 min at the same temperature, warmed up to room temperature and stirred for 16 hr. The reaction solution was filtered, washed with dichloromethane, and concentrated in vacuo. The residue was poured into water/ethyl acetate for partition. The organic layer was washed with brine, dried over MgSO₄ and concentrated in vacuo. The residue was

15 subjected to silica gel column chromatography and fractions eluting with toluene/ethyl acetate (1:1 to ethyl acetate) were collected to obtain an N-benzyl compound (10.654 g, yield 54.6%) as an oil.

IR (CHCl₃): 3320,1741,1646,1488,1434.

NMR (CDCl₃): 1.86-2.06 (m, 1H), 2.28-2.48 (m, 1H), 3.30-3.50 (m, 2H), 3.51-3.80 (m, 3H), 3.61 (s, 2H), 3.72 (s, 3H), 4.37-4.53 (m, 1H), 7.14 (d, J=9Hz, 2H), 7.42 (d, J=9Hz, 2H), 7.20-7.39 (m, 5H).

20 (6) 57->58

To a solution of the N-benzyl compound (10.782 g, 25.00 mmol) in dichloromethane were added di-t-butyl dicarbonate

25 (12.42 g, 2.2 x 25.00 mmol) and then 4-dimethylaminopyridine (640 mg, 0.4 x 25.00 mmol) under ice-cooling. The mixture was stirred for 10 min at the same temperature, then warmed up to room temperature and stirred for 22 hr. The reaction solution was



poured into water/dichloromethane containing dil. HCl for partition. The dichloromethane layer was washed with water, saturated aqueous sodium bicarbonate, and water, dried over MgSO_4 and concentrated in vacuo. The residue was subjected to silica
5 gel column chromatography and fractions eluting with toluene/ethyl acetate (3:1) were collected to obtain a Boc-compound as a foam (5.412 g). Yield 42.7%.

IR (CHCl_3): 1792, 1744, 1684, 1648, 1489, 1474, 1450, 1426.

NMR (CDCl_3): 1.047 (s, 9H), 1.88-2.14 (m, 1H), 2.22-2.50 (m, 1H),
10 3.24-3.75 (m, 3H), 3.54 (s, 2H), 3.70 (s, 3H), 4.23-4.55 (m, 1H), 4.40 (s, 2H), 7.03 (d, $J=9\text{Hz}$, 2H) 7.41 (d, $J=9\text{Hz}$, 2H), 6.98-7.35 (m, 5H).

(7) 58->59

To a solution of methyl ester (5.410 g, 10.180 mmol)
15 in methyl alcohol (67 ml) was added 1 N potassium hydroxide aqueous solution (20.3 ml, 2 x 10.180 mmol) and the mixture stirred for 2 hr and 35 min at room temperature. The reaction solution was poured into water/ethyl ether for partition. The ethyl ether layer was washed with water. Aqueous layers were combined and poured
20 into water/ethyl acetate containing dil. HCl for partition. The organic layer was washed with water, dried over MgSO_4 and concentrated in vacuo to obtain a carboxylic acid (4.434 g) as a foam. Yield 84.2%.

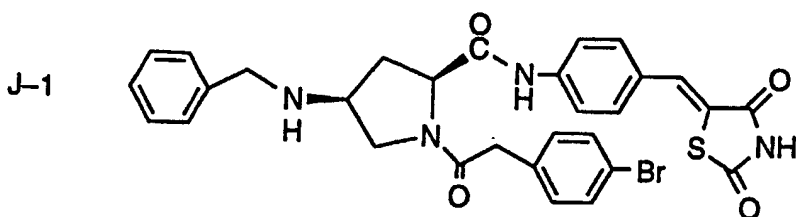
IR (CHCl_3): 3350, 2600, 1728, 1683, 1647, 1487, 1474, 1451, 1417, 1392.

25 NMR (CDCl_3): 1.41 (s, 9H), 2.10-2.45 (m, 2H), 3.29 (t, $J=10\text{Hz}$, 1H), 3.40-3.72 (m, 1H), 3.56 (s, 2H), 4.24-4.56 (m, 4H), 5.40-6.00 (m, 1H), 7.03 (d, $J=9\text{Hz}$, 2H), 7.39 (d, $J=9\text{Hz}$, 2H), 7.07-7.19 (m, 2H), 7.21-7.35 (m, 3H).

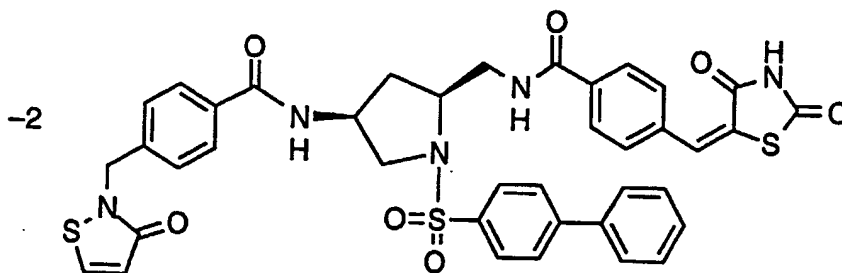


The product was treated in a manner similar to those described in the Examples above to yield thiazolidinedione derivative(J-1). The Physicochemical values of the compound (J-1) are shown in Table below.

5 Table J

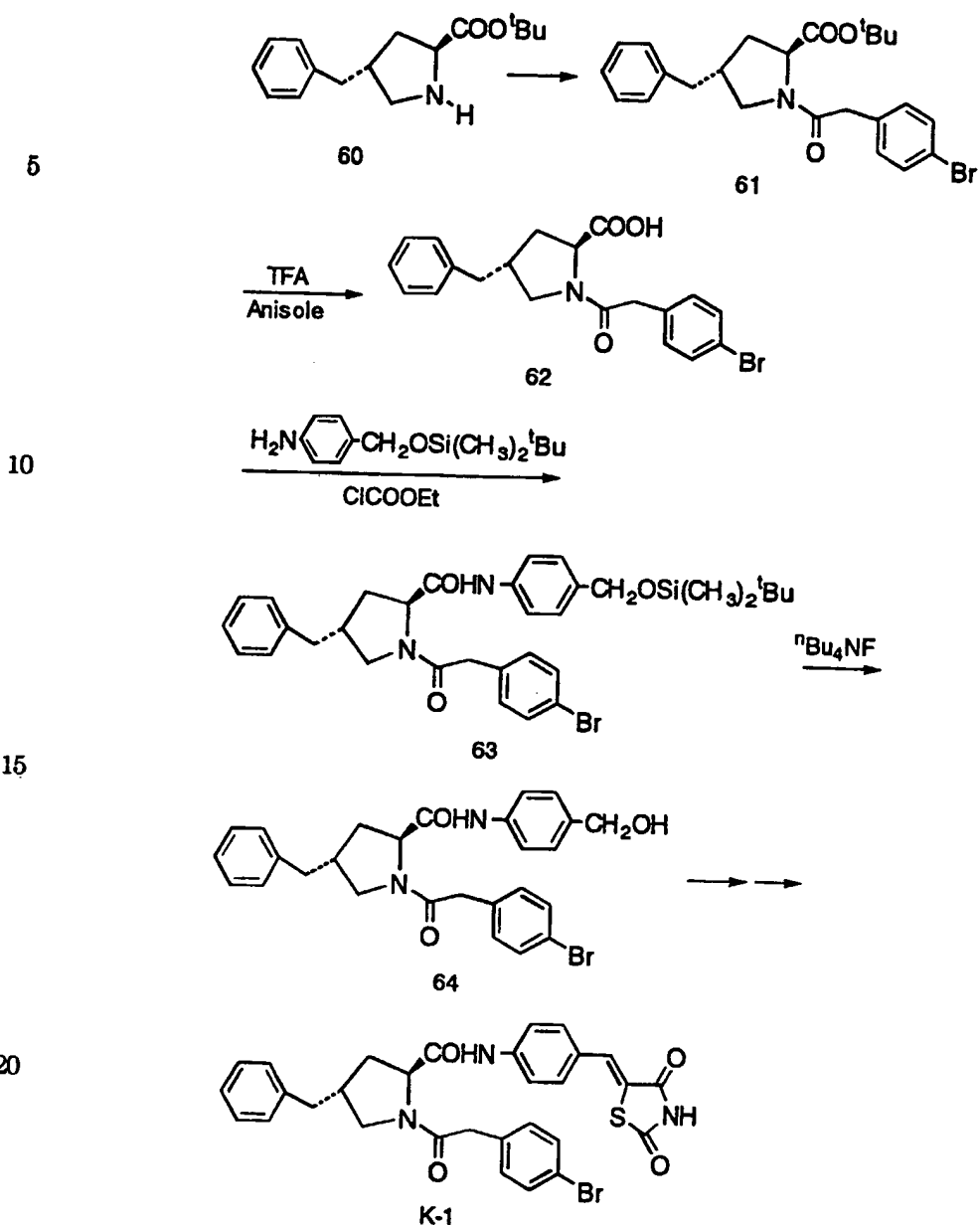


IR(CHCl ₃ cm ⁻¹)	NMR(CDCl ₃ ppm)
1738	4.60(m,1H)
1702	4.73(d,1H)
1632	
1590	



IR(Nujol cm ⁻¹)	NMR(DMSO ppm)
1739	4.92(s,-CH ₂ -)
1701	7.26(s,-CH=)
1626	10.42(s,NH)



Example 14 (Method K)(1) 60 \rightarrow 61

25

To a solution of the starting compound (0.39 g, 1.49 mmol), which is described in a literature (D. K. Dikshit and S. K. Panday, J. Org. Chem., 1992, 57, 1927), in methylene chloride (5 ml) were added triethylamine (0.62 ml, 4.48 mmol) and 4-



bromophenylacetic acid (0.35 g, 1.63 mmol). To the mixture was added 2-chloro-1,3-dimethylimidazolinium chloride (0.38 g, 2.24 mmol) with stirring and under ice-cooling. After stirring for 1 hr at room temperature, the mixture was poured into ice-cold water, followed by extraction with ethyl acetate. The organic layer was washed with 1N HCl, saturated aqueous solution of NaHCO₃, brine, successively, dried over anhydrous Na₂SO₄, and concentrated in vacuo. The residue was purified with silica gel column chromatography (toluene/ethyl acetate, 85:15) to obtain an aimed product (0.52 g). Yield 76%.

Elemental analysis (C₂₄H₂₈BrNO₃)

Calcd.: C, 62.89; H, 6.16; N, 3.06

Found : C, 63.06; H, 6.24; N, 3.16

NMR (CDCl₃): 1.43 (s, 9H), 1.97 (m, 2H), 2.62 (m, 3H), 3.15 (m, 1H), 3.58 (s, 2H), 3.63 (m, 1H), 4.43 (dd, 1H, J=4.0, 8.6Hz), 7.01-7.50 (m, 9H).

(2) 61->62

To a solution of a starting compound (0.52 g, 1.13 mmol) in methylene chloride were added anisole (0.62 ml, 5.71 mmol) and trifluoroacetic acid (0.85 ml, 11.4 mmol) and the mixture allowed to stand overnight at room temperature. Under ice-cooling, the reaction mixture was combined with aqueous solution of NaHCO₃ and concentrated. The residue was extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous Na₂SO₄, and concentrated in vacuo. The residue was subjected to silica gel column chromatography and fractions eluting with chloroform/methanol/acetic acid (94:6:0.1) were collected to obtain an aimed product (0.44 g).



Elemental analysis ($C_{24}H_{28}BrNO_3$)

Calcd.: C, 62.89; H, 6.16; N, 3.06

Found : C, 63.06; H, 6.24; N, 3.16.

NMR ($CDCl_3$): 1.81 (m, 1H), 2.46 (m, 1H), 2.70 (m, 3H), 3.17 (m,
5 1H), 3.61 (m, 1H), 3.63 (s, 2H), 4.65 (d, 1H, $J=7.2\text{Hz}$), 7.10-7.51
(m, 9H).

(3) 62-→63

Under a nitrogen atmosphere, to a solution of a
starting compound (0.45 g, 1.11 mmol) and triethylamine (0.37 ml,
10 2.68 mmol) in methylene chloride (5 ml) was added ethyl
chlorocarbonate (0.19 ml, 2.0 mmol) under ice-cooling, and the
mixture stirred for 1 hr. After the addition of a solution of
4-(dimethyl-t-butylsilyloxymethyl)aniline (0.32 g, 1.33 mmol) in
methylene chloride (1 ml), the mixture was stirred for 3 hr under
15 ice-cooling . To the reaction mixture was added water, followed
by extraction with ethyl acetate. The organic layer was washed
with 1N HCl, saturated aqueous $NaHCO_3$, and brine, successively, dried
over Na_2SO_4 , and concentrated. The residue was subjected to silica
gel column chromatography and the fractions eluting with ethyl
20 acetate/toluene (2:8) were collected to yield an aimed product
(0.59 g). Yield 86%.

Elemental Analysis ($C_{33}H_{41}BrN_2O_3Si \cdot 0.5H_2O$)

Calcd.: C, 62.85; H, 6.71; N, 4.44

Found : C, 62.77; H, 6.61; N, 4.61.

25 NMR ($CDCl_3$): 0.07 (s, 6H), 0.92 (s, 9H), 1.60 (m, 1H), 2.65 (m,
1H), 2.86 (m, 2H), 3.15 (t, 1H, $J=9.0\text{ Hz}$), 3.55 (m, 1H), 3.61 (s,
2H), 4.68 (s, 2H), 4.82 (d, 1H, $J=7.8\text{ Hz}$), 7.07-7.50 (m, 13H), 9.43 (s,
1H).



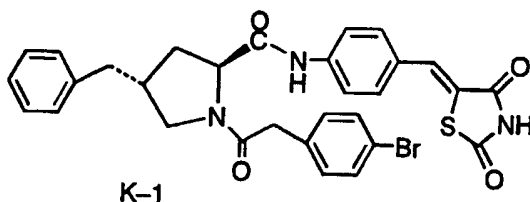
(4) 63->64

To a solution of a starting compound (0.27 g, 0.434 mmol) in tetrahydrofuran (3 ml) was added 1M tetrabutylammonium fluoride in tetrahydrofuran (0.434 ml, 0.434 mmol), and the mixture
 5 allowed to stand overnight. The mixture was concentrated in vacuo and extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous Na_2SO_4 , and concentrated in vacuo. The residue was subjected to silica gel column chromatography and the fractions eluting with ethyl acetate/toluene (6:4) were collected
 10 to yield an aimed product (0.15 g). Yield 67%.

NMR (CDCl_3): 1.60 (m, 1H), 2.63 (m, 2H), 2.84 (m, 2H), 3.16 (t, 1H, $J=9.4$), 3.59 (m, 1H), 3.61 (s, 2H), 4.62 (s, 2H), 4.82 (d, $J=7.8\text{Hz}$, 1H), 7.08-7.50 (m, 13H), 9.51 (s, 1H).

The thiazolidinedione derivative(K-1) was then
 15 prepared in a manner similar to that described in preceding Examples. Physicochemical values thereof are shown in Table below.

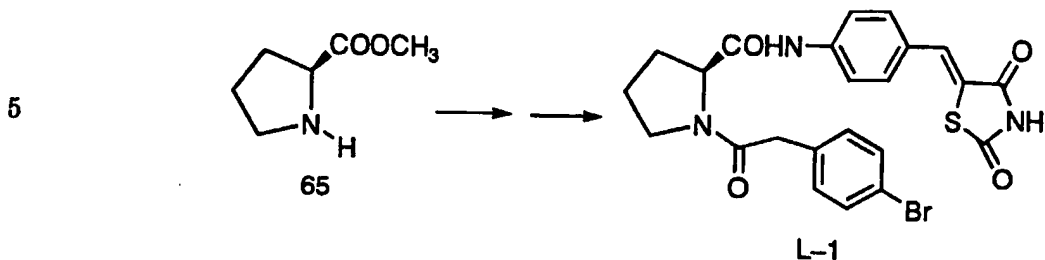
Table K



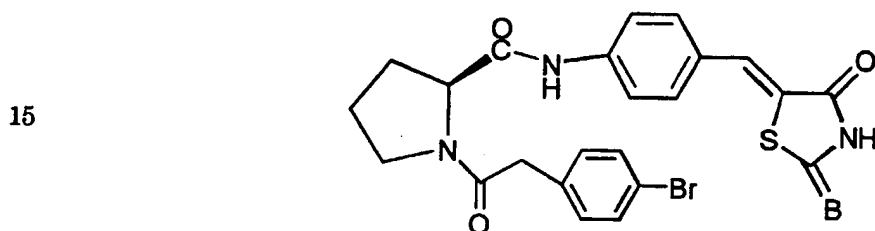
IR(CHCl_3 cm^{-1})	NMR(CDCl_3 ppm)
1743	
1704	3.63(s, $-\text{CH}_2-$)
1629	7.70(s, $-\text{CH}=\text{N}-$)
1586	

25



Example 15 (Method L)

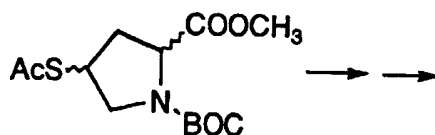
Compounds having proline ring instead of pyrrolidine
 were prepared in a manner similar to that described in preceding
 10 Examples. Physicochemical values thereof are shown in Table L.

Table L

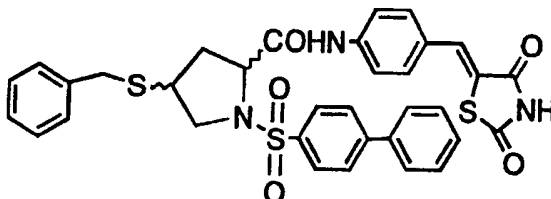
20

	B	IR(Nujol cm^{-1})	NMR(CDCl_3 ppm)
L-1	S	1700 1584 1530	3.72(s, $-\text{CH}_2-$) 7.91(s, $-\text{CH}=\text{)$
-2	O	1746 1700 1678	3.71(s, $-\text{CH}_2-$) 7.70(s, $-\text{CH}=\text{)$



Example 16 (Method M)

5



10

	4-Position	2-Position		4-Position	2-Position
66a	AcS-----	COOCH ₃	N-1	BnS-----	CONH-
b	AcS-----	COOCH ₃	N-2	BnS-----	CONH-
c	AcS-----	COOCH ₃	N-3	BnS-----	CONH-
3	AcS-----	COOCH ₃	A-42	BnS-----	CONH-

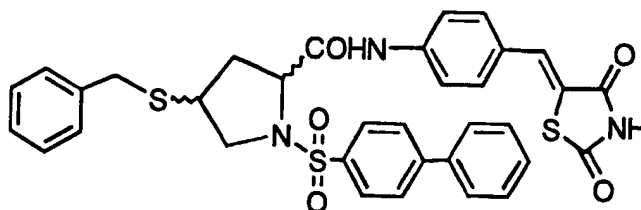
15

In this Example, three kinds of compound, which correspond to Compound A-42, with different configuration at 2- and 4-positions of pyrrolidine ring were prepared in a manner similar to that described in preceding Examples using a starting compound known in Japanese Patent Publication (KOKAI) No.

20 294970/1993 (USP 5317016). Physicochemical values of the resultant compounds are shown in Table M.



Table M



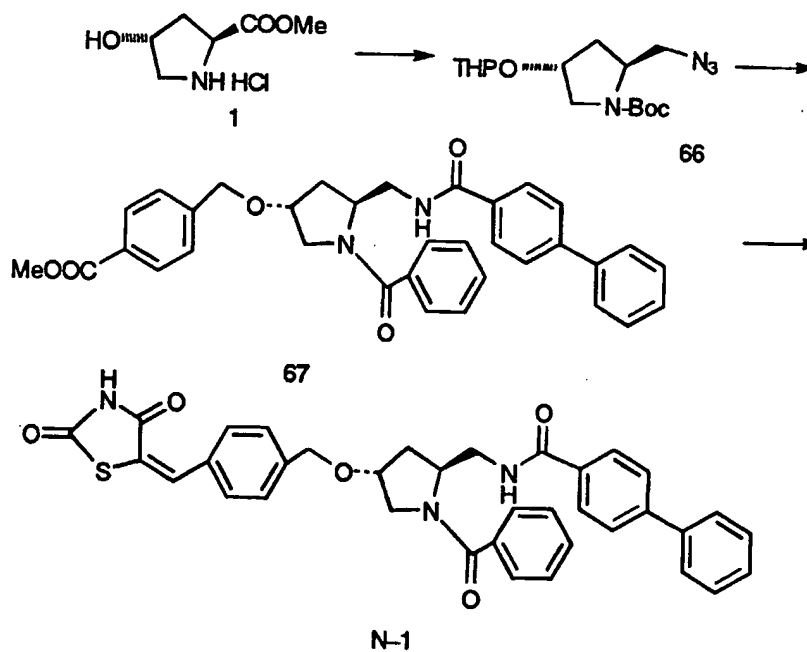
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10

	Position 2 4		IR(Nujol cm ⁻¹)	NMR(CDCl ₃ ppm)
M-1	2β	4α	3361 1599 3145 1758 1685	3.68(s,-CH ₂ -) 7.82(s,-CH=)
-2	2α	4β	3360 1598 3139br 1751 1685	3.69(s,-CH ₂ -) 7.82(s,-CH=)
-3	2α	4α	3550 1588 1750 1697 1664	3.68(s,-CH ₂ -) 7.82(s,-CH=)

15

Example 17 (Method N)

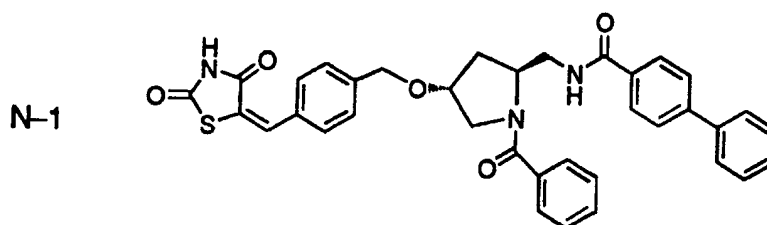


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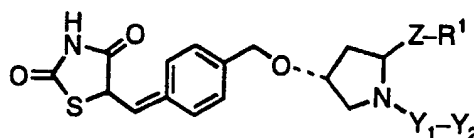
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The compound (66) was prepared using the compound (1) as a starting material in accordance with the method described in preceding Examples. The compound (66) was then converted into compound (67) in accordance with the procedures described in preceding Examples, which involve the steps: etherification at the 4-position; reduction at the 2-position; amidation; deprotection at the 1-position; and amidation. The compound (67) was treated in a manner similar to that described in Examples above to yield the compound N-1.

10 Table N-1

IR (KB r cm ⁻¹)	NMR (CDC l ₃ ppm)
1743	4.39(ABd, -CH ₂ -)
1705	4.49(ABd, -CH ₂ -)
1608	7.81(s, -CH=)



	Z	R¹	Y₁-Y₂
N-2	CH ₂ NHCO		CO-
N-3	.		CO-
N-4	.		SO ₂ -
N-5	.		CONH(CH ₂) ₃ CH ₃
N-6	.	-(CH ₂) ₃ CH ₃	SO ₂ -
N-7	.		SO ₂ (CH ₂) ₃ CH ₃



Compounds prepared in Examples above were tested for the cPLA₂ inhibitory activity in a manner shown in the following experimental example.

5 Experiment 1 cPLA₂ Inhibitory activity

The compounds of the present invention was tested for the cPLA₂ inhibitory activity by a method known in a literature (R. M. Kramer, E. F. Roberts, J. Manetta and J. E. Putnam, J. Biol. Chem., 268(8), 5268-5272 (1991)), as outlined below.

10 As a substrate, liposomes which contain 1-palmitoyl-2-[¹⁴C]-arachidonoyl-sn-glycero-3-phosphocholine and sn-1,2-dioleoylglycerol at the ratio of 2:1 and have treated ultrasonically were used. The substrate was added to a 50 mM HEPES buffer (pH 7.4) (200 µl) containing 1 mM CaCl₂, 2 mM dithiothreitol,
15 150 mM NaCl, 0.1 mg/ml BSA so as to make the concentration of radio-labeled phosphatidylcholine 2.5 µM. To the solution was added a compound of the present invention in DMSO (10 µl) to obtain reaction solutions each containing the test compound at 250 µM, 50 µM, 10 µM, 2 µM, and 0.4 µM. The reaction was allowed to start
20 by adding an enzyme (cPLA₂) (4 ng) and continued for 15 min at 37°C.

The amount of fatty acids released by the reaction was measured on a liquid scintillation counter. Control was obtained by conducting the experiment in the same manner except that a compound of the present invention was not added. The
25 inhibitory activity was expressed as percent (%) to the control value, which was used for the calculation of the concentration required for 50% inhibition (IC₅₀, µM). The results are shown in Table P.



Table P cPLA₂ Inhibition Activity

Compound No.	IC ₅₀ (μ M)	Compound No.	IC ₅₀ (μ M)	Compound No.	IC ₅₀ (μ M)
A-2	7.2	A-22	21	A-42	14
A-3	5.3	A-23	10	A-43	6.8
A-4	1.6	A-24	9.2	A-44	7.4
A-5	3.6	A-25	18	A-45	4.8
A-6	3.3	A-26	2.8	A-46	7.0
A-7	5.3	A-27	5.1	A-47	6.0
A-8	4.8	A-28	8.3	A-48	4.9
A-9	5.1	A-29	5.9	A-49	17
A-10	3.8	A-30	16	A-50	12
A-11	4.7	A-31	4.8	A-51	6.3
A-12	1.3	A-32	4.8	A-52	5.6
A-13	20	A-33	6.4	A-54	3.4
A-14	18	A-34	6.3	A-55	3.4
A-15	15	A-35	19	A-56	1.9
A-16	22	A-36	14	A-57	4.7
A-17	6.0	A-37	16	A-58	5.1
A-18	16	A-38	6.4	A-59	8.6
A-19	4.3	A-39	6.2	A-60	6.1
A-20	22	A-40	15	A-61	16
A-21	18	A-41	3.4	A-62	4.3
				A-63	3.2
B-1	0.82	E-1	1.1	H-1	6.7
B-2	2.9	E-2	0.46	H-2	8.1
B-3	1.2	E-3	0.85	H-3	14
B-4	2.4	E-4	3.7	H-4	26
B-5	22	E-5	7.7	H-5	6.4
B-6	31	F-2	10	H-6	17
B-7	9.7	G-1	9.0	H-7	11
B-8	1.3	G-2	20	H-8	3.2
B-9	0.44	G-3	17	H-9	2.0
C-1	30	G-4	14	H-10	10
C-2	25	G-5	21	H-11	4.3
C-3	16	G-6	10	H-12	6.2
C-4	3.2	G-8	5.6	H-13	4.4
C-5	9.8	G-9	4.2	H-14	8.2
C-6	13	G-10	6.0	H-15	11
D-1	22	G-10	6.0	H-16	4.3
D-2	7.0	G-11	8.5	H-17	4.9
		G-12	9.9	H-18	11
				H-19	8.6
				H-20	6.6



Table P cPLA₂ Inhibitory activity (Continued)

Compound No. IC ₅₀ (μM)		Compound No. IC ₅₀ (μM)		Compound No. IC ₅₀ (μM)	
5	I-1	2	6		
	I-2	3	5		
	J-1	2	1		
	J-2	2	9		
	L-1	5	3		
	M-1	2	3		
	M-2	1	5		
	M-3	1	0		
	N-1	6	6		

10

Experiment 2 Inhibition of Production of Prostaglandin E₂ in Human Fibroblasts

Proliferation of fibroblasts has been observed in lesion sites of patients suffering from rheumatoid arthritis, indicating that prostaglandins produced by fibroblasts, under the stimulation of inflammatory cytokines such as TNF or IL-1, could participate in the progress of the pathological conditions of disease. From this viewpoint, the compounds of the present invention were tested for the effect on the production of prostaglandin E₂ by human fibroblasts under the stimulation with IL-1 according to the method of J.M.Dayer et al (CACHECTIN/TUMOR NECROSIS FACTOR STIMULATES COLLAGENASE AND PROSTAGLANDIN E₂ PRODUCTION BY HUMAN SYNOVIAL CELLS AND DERMAL FIBROBLASTS; J.M. Dayer, B. Beutler and A. Cerami, J. Exp. Med., 162,2163-2168, 1985).

As shown in Table Q, the production of prostaglandin E₂ was significantly inhibited.



Table Q Inhibitory activity Against the Production of
Prostaglandin E₂ in Human Fibroblasts

Compound No. IC ₅₀ (μM)		Compound No. IC ₅₀ (μM)		Compound No. IC ₅₀ (μM)		
15	A-3	2.4	A-30	0.51	B-1	7.5
	A-4	4.9	A-37	6.9	B-2	1.9
	A-5	7.0	A-38	4.9	B-3	2.1
	A-6	8.2	A-39	6.0	B-4	4.6
	A-7	4.5	A-40	7.7	B-5	2.0
	A-8	2.5	A-41	14	B-6	4.7
	A-9	3.0	A-42	3.8	B-7	3.6
	A-11	8.5	A-43	8.8	C-1	6.1
	A-12	1.6	A-44	1.5	C-2	0.40
	A-16	2.9	A-45	1.5	C-3	7.4
20	A-17	3.2	A-46	1.5	C-4	2.0
	A-20	0.30	A-48	8.7	C-5	1.2
	A-21	1.0	A-52	2.9	C-6	2.3
	A-23	8.6	A-53	0.83	D-1	3.6
	A-24	4.9	A-54	1.1	D-2	5.7
	A-25	8.0	A-55	1.1	D-3	7.1
	A-26	1.8	A-56	0.93	E-2	6.0
	A-27	2.6	A-60	1.3	E-4	1.9
	A-28	0.73	A-61	10	H-8	9.9
	A-29	1.2	A-62	2.2	H-9	9.6
25				H-10	2.4	
				H-11	8.5	
				H-16	1.9	
				H-17	7.0	
				H-18	1.5	
			J-2	9.7		



Industrial Utility

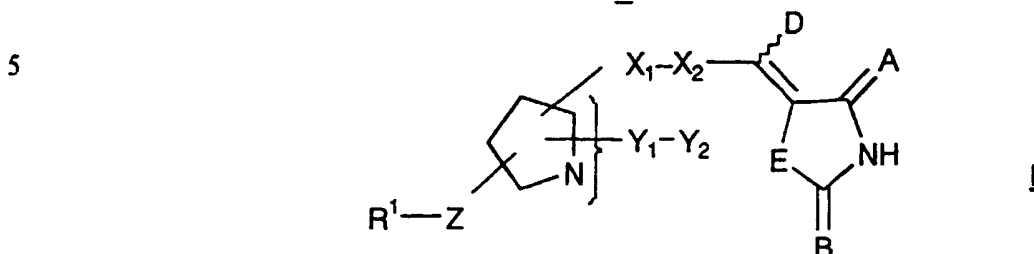
The compounds of the present invention are capable of inhibiting the activity of cytosolic phospholipase A₂ and the production of prostaglandin E₂, and are useful in the prevention
5 or treatment of inflammatory diseases such as rheumatoid arthritis, asthma, inflammatory bowel disease, injury due to ischemic reperfusion, allergic rhinitis, and psoriasis.



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THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A compound of the formula I:

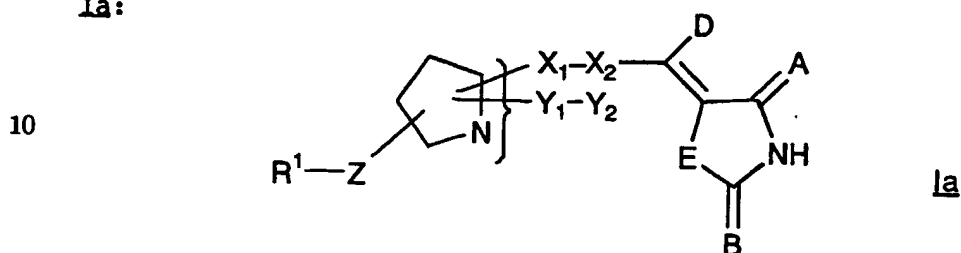


10 wherein A and B are independently O or S; E is O or S; X₁ is -
CO-, -CONH-,
-CH₂NHSO₂-, -CH₂NHCO-, -CH₂NHCS-, -CH₂O-, -OCH₂-, -CH₂OCH₂-, C₁-
C₁₅ alkylene, C₂-C₁₀ alkenylene or a single bond; X₂ is
optionally substituted phenylene or naphthalene, optionally
15 substituted indol-diyl or a single bond; D is hydrogen or
hydroxy C₁-C₁₅ alkyl; Y₁ is -(CH₂)_mCO-, -(CH₂)_nNHCO-, -
(CH₂)_nNHSO₂-, -(CH₂)_mCONH-, -(CH₂)_mCSNH-, -(CH₂)_mSO₂-, -
(CH₂)_mCOO-, or a single bond; m and n are an integer of 0 to
3; Y₂ is hydrogen, C₁-C₁₅ alkyl, optionally substituted C₂-C₁₀
20 alkenyl, optionally substituted C₃-C₁₂ cycloalkyl, optionally
substituted C₃-C₁₂ cycloalkenyl, optionally substituted C₃-C₁₂
cycloalkyl C₁-C₁₅ alkyl, optionally substituted C₃-C₁₂
cycloalkenyl C₁-C₁₅ alkyl, optionally substituted aryl,
optionally substituted aryl C₁-C₁₅ alkyl, optionally
25 substituted cyclic group containing one or more hetero atoms
selected from the group consisting of oxygen, sulfur and
nitrogen atoms on the ring, and is optionally condensed with a
carbon ring or optionally substituted amino; Z is -S-, -SO-, -
O-, -NH-, -CONH-, -CONHCH₂- or a single bond; R¹ is hydrogen,
30 optionally substituted C₁-C₁₅ alkyl, optionally substituted C₂-
C₁₀ alkenyl, optionally substituted aryl or optionally
substituted aryl C₁-C₁₅ alkyl, or a pharmaceutically
acceptable salt or a hydrate thereof, provided that when X₁ is
-CH₂O-, Y₁ is not a single bond; Y₁ binds to the pyrrolidine
35 ring at 1- or 2-position, X₁ binds to any positions other than
the one to which Y₁ binds (provided that when Y₁ is at the 2-
position, X₁ binds to



the 1-position), and Z binds to any one of carbon atoms on the pyrrolidine ring other than those to which X_1 and Y_1 bind; when Y_1 binds to the N-atom on the pyrrolidine ring, n is not 0; when Y_1 is $-(CH_2)_mCOO^-$ and m is 0, Y_2 is not hydrogen atom; and when X_1 is $-OCH_2-$, it does not bind to the N-atom on the pyrrolidine ring.

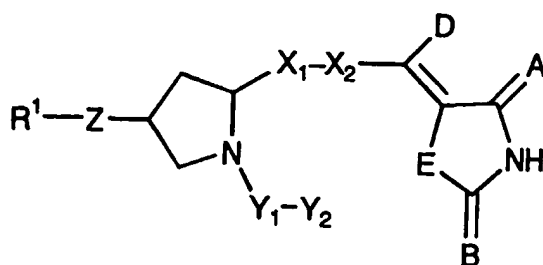
2. The compound of claim 1 which is shown by the formula Ia:



wherein A, B, E, X_1 , X_2 , D, Y_1 , Y_2 , Z and R^1 are as defined above, or a pharmaceutically acceptable salt or a hydrate thereof, provided that when X_1 is $-CH_2O-$, Y_1 is not a single bond; Y_1 binds to the pyrrolidine ring at the 1- or 2-position, and when Y_1 binds to the 1-position, X_1 binds to the 2-position, and when Y_1 binds to the 2-position, X_1 binds to the 1-position, and Z binds to any one of carbon atoms on the pyrrolidine ring other than those to which X_1 and Y_1 bind; when Y_1 binds to the N-atom on the pyrrolidine ring, n is not 0; when Y_1 is $-(CH_2)_mCOO^-$ and m is 0, Y_2 is not hydrogen atom; and when X_1 is $-OCH_2-$, it does not bind to the N-atom on the pyrrolidine ring.

25 3. The compound of claim 1 or 2 which shown by the formula Ib:



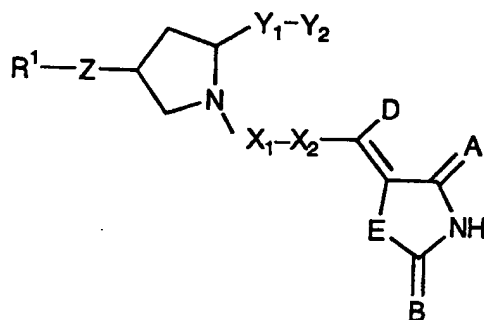
b

5

wherein A, B, E, X₁, X₂, D, Y₁, Y₂, Z and R¹ are as defined above,
or a pharmaceutically acceptable salt or a hydrate thereof,
provided that when X₁ is -CH₂O-, Y₁ is not a single bond; n is not
0; when Y₁ is -(CH₂)_mCOO- and m is 0, Y₂ is not hydrogen atom.

10

4. The compound of claim 1 or 2 which is shown by the
formula Ic:

Ic

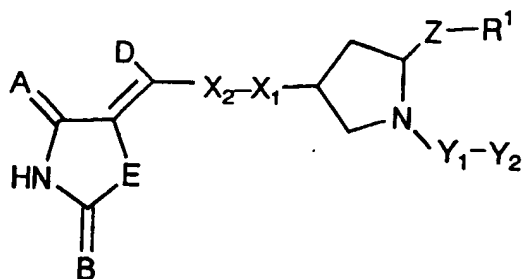
15

wherein A, B, E, X₁, X₂, D, Y₁, Y₂, Z and R¹ are as defined above,
or a pharmaceutically acceptable salt or a hydrate thereof,
provided that when X₁ is -CH₂O-, Y₁ is not a single bond; when X₁
is -OCH₂-, it does not bind to the N-atom on pyrrolidine ring.

5. The compound of claim 1 or 2 which is shown by the
formula Id:

25



Id

5

wherein A, B, E, X_1 , X_2 , D, Y_1 , Y_2 , Z and R^1 are as defined above, or a pharmaceutically acceptable salt or a hydrate thereof, provided that when X_1 is $-\text{CH}_2\text{O}-$, Y_1 is not a single bond; n is not 0; when Y_1 is $-(\text{CH}_2)_m\text{COO}-$ and m is 0, Y_2 is not hydrogen atom.

10

6. The compound of any one of claims 1 to 5, wherein E is S, and A and B is O, or a pharmaceutically acceptable salt or a hydrate thereof.

15

7. The compound of any one of claims 1 to 5, wherein X_1 is $-\text{CONH}-$, $-\text{CH}_2\text{NHSO}_2-$ or $-\text{CH}_2\text{NHCO}-$, or a pharmaceutically acceptable salt or a hydrate thereof.

8. The compound of any one of claims 1 to 5, wherein X_2 is optionally substituted phenylene, or a pharmaceutically acceptable salt or a hydrate thereof.

9. The compound of any one of claims 1 to 5, wherein Y_1 is $-\text{CO}-$, $-\text{CONH}-$ or $-\text{SO}_2-$, or a pharmaceutically acceptable salt or a hydrate thereof.



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10. The compound of any one of claims 1 to 5, wherein Y_2 is optionally substituted C_3-C_{12} cycloalkenyl C_1-C_{15} alkyl, optionally substituted aryl, optionally substituted aryl C_1-C_{15} alkyl or optionally substituted cyclic group containing one or 5 more hetero atoms selected from the group consisting of oxygen, sulfur and nitrogen atoms on the ring, and is optionally condensed with a carbon ring, or a pharmaceutically acceptable salt or a hydrate thereof.

10 11. The compound of any one of claims 1 to 5, wherein Z is -S- or -O-, or a pharmaceutically acceptable salt or a hydrate thereof.

12. The compound of any one of claims 1 to 5, wherein R^1 is 15 optionally substituted C_1-C_{15} alkyl or optionally substituted aryl C_1-C_{15} alkyl, or a pharmaceutically acceptable salt or a hydrate thereof.

13. A pharmaceutical composition containing a compound of 20 claim 1 and a pharmaceutically acceptable carrier.

14. Use of a compound of claim 1 in the preparation of a medicament for the inhibition of phospholipase A_2 .

25 15. Use of a compound of claim 1 in the preparation of a medicament for the inhibition of the production of prostaglandin E_2 .

16. A method for the inhibition of phospholipase A_2 30 including the step of administering to a patient in need thereof a pharmaceutically effective amount of a compound of claim 1.

17. A method for the inhibition of the production of 35 prostaglandin E_2 including the step of administering to a patient in need thereof a pharmaceutically effective amount of a compound of claim 1.



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18. A compound according to claim 1 or 2 substantially as
hereinbefore described with reference to the Examples.

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DATED this 11th day of May, 1999.

SHIONOGI & CO. LTD.

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by DAVIES COLLISON CAVE
Patent Attorneys for the Applicant

